

Reimbursement Review

Bimekizumab (Bimzelx)

Sponsor: UCB Canada Inc.

Therapeutic area: Hidradenitis suppurativa

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Clinical Review

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Abbreviations

AE	adverse event
AN	abscess and inflammatory nodule
CDA-AMC	Canada's Drug Agency
CI	confidence interval
CrI	credible interval
CSPA	Canadian Skin Patient Alliance
DLQI	Dermatology Life Quality Index
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HiSCR	Hidradenitis Suppurativa Clinical Response
HiSCR50	Hidradenitis Suppurativa Clinical Response 50
HiSCR75	Hidradenitis Suppurativa Clinical Response 75
HiSCR90	Hidradenitis Suppurativa Clinical Response 90
HiSCR100	Hidradenitis Suppurativa Clinical Response 100
HiSQOL	Hidradenitis Suppurativa Quality of Life
HRQoL	health-related quality of life
HS	hidradenitis suppurativa
HS Support Group	Hidradenitis & Me Support Group
HSSDD	Hidradenitis Suppurativa Symptom Daily Diary
IBD	inflammatory bowel disease
LS	least squares
MAIC	matching-adjusted indirect comparison
MCID	minimal clinically important difference
MI	multiple imputation
MID	minimal important difference
MCMC	Markov Chain Monte Carlo
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	odds ratio
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SLR	systematic literature review

TEAE	treatment-emergent adverse event
TNF	tumour necrosis factor

Executive Summary

An overview of the submission details for the drug under review is provided in [Table 1](#).

Table 1: Background Information of Application Submitted for Review

Item	Description
Drug product	Bimekizumab (Bimzelx), solution for injection (160 mg/1 mL prefilled syringe or autoinjector)
Sponsor	UCB Canada Inc.
Indication	The treatment of adult patients with moderate to severe hidradenitis suppurativa with an inadequate response to conventional systemic therapy.
Reimbursement request	For treatment of adult patients with moderate to severe hidradenitis suppurativa who have inadequate response to conventional systemic therapy.
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	December 12, 2025
Recommended dose	The recommended dose of Bimzelx for adult patients with hidradenitis suppurativa is 320 mg (given as 2 subcutaneous injections of 160 mg or 1 subcutaneous injection of 320 mg) every 2 weeks up to week 16 and every 4 weeks thereafter.

NOC = Notice of Compliance.

Introduction

Hidradenitis suppurativa (HS) is a chronic, systemic, and debilitating inflammatory skin disease resulting from hair follicle occlusion, which results in a cycle of chronic inflammation, abscess formation, and inflamed nodules with draining tunnels and scarring.^{1,2} Symptoms of HS include pain, itch, skin damage, infection, odorous secretions, and physical/movement limitations; these can interfere with physical functioning, activities of daily living, work, and productivity.³⁻⁶ HS substantially impacts health-related quality of life (HRQoL) including factors such as mental well-being and sexual dysfunction,^{3,7} and is also associated with comorbidities such as psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, inflammatory bowel disease (IBD), polycystic ovarian syndrome, diabetes mellitus, thyroid disease, obesity, metabolic syndrome, acne, and pyoderma gangrenosum.^{8,9} The prevalence of HS in Canada is estimated to be up to 3.8% of the general population, based on a 2016 survey.^{8,10} A single-centre chart review conducted in Canada reported that 55% of patients had mild HS and 45% had moderate to severe HS upon diagnosis.¹¹ HS is diagnosed based on clinical presentation, without the use of any biological or pathological tests for diagnosis.^{3,9} The Dessau criteria are used to diagnose HS by characterizing recurrent, painful, or suppurating nodules that are present on 2 or more occasions within 6 months.^{8,9}

In Canada, treatment guidelines recommend personalizing treatments for the management of HS based on the patient's needs and disease stage (i.e., mild, moderate, or severe according to the Hurley system).⁸ Topical therapies (e.g., skin cleansers, resorcinol, and antibiotics) are recommended for mild HS cases in addition to conventional systemic treatments (e.g., oral antibiotics, oral retinoids, oral contraceptives, or spironolactone) for patients with mild disease who are considered refractory to topical therapies.⁸ In cases of

suboptimal or inadequate response to conventional systemic treatments, patients with moderate to severe HS (Hurley stage II or III) may receive biologic therapy; for severe HS, early initiation of biologic therapy is recommended.⁸ Adalimumab and secukinumab are currently approved for the treatment of HS in Canada, with Canadian guidelines also recommending off-label infliximab as a second-line biologic option and off-label ustekinumab or off-label anakinra as third-line biologic options for treating HS.⁸ In addition to the medical treatments, patients may concurrently undergo laser, procedural, and/or surgical treatments, which generally increase in invasiveness with HS severity.^{8,12,13}

The objective of this clinical review report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of bimekizumab (320 mg given as 2 subcutaneous injections of 160 mg or 1 subcutaneous injection of 320 mg, every 2 weeks up to week 16 and every 4 weeks thereafter) for adult patients with moderate to severe HS. Bimekizumab has previously been reviewed by Canada's Drug Agency (CDA-AMC) for the treatment of psoriasis, psoriatic arthritis, and ankylosing spondylitis.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups responding to the CDA-AMC call for input and from the clinical experts consulted for the purpose of this review.

Patient Input

The Canadian Skin Patient Alliance (CSPA) and the Hidradenitis & Me Support Group (HS Support Group) collaboratively provided input for this review. CSPA is a national charity organization with the aim of improving the health and well-being of people in Canada who are affected by skin, hair, and nail conditions, through collaboration, advocacy, and education. The HS Support Group provides a safe space for individuals with HS to connect, share experiences, and learn about the condition. Information was gathered for this input submission through patient responses from 3 surveys: the CSPA's *Scarred for Life: 2020 Update. A National Report of Patients' Experiences Living with Hidradenitis Suppurativa*, the Health Policy Partnership's 2024 *Call to Action: Improving the Lives of People With Hidradenitis Suppurativa (HS) in Canada*, and a patient survey hosted by the patient groups from March 28, 2023, to May 23, 2023. The 2020 survey gathered responses from 537 individuals with HS, of whom 14% were from Canada, 12% from the UK, and 50% from the US. There was representation from across Canada, with the majority of respondents from Ontario (41%) and Alberta (18%). In total, 15 responses were received from the 2023 survey, with all the respondents from Canada and the majority from Ontario (47%) and Alberta (27%). In addition, the HS Support Group gathered information, through a post in a Facebook group of Canadians with HS, on the experiences of individuals who have received bimekizumab; 4 patients with relevant experience submitted responses.

Survey respondents indicated that HS has a profoundly negative impact on their mental and physical health, social interactions, ability to carry out activities of daily living, intimacy, and work performance. The respondents also highlighted specific concerns such as body odour, clothing stains, and the unpredictable nature of disease flares. All respondents to the 2023 survey noted that their HS lesions are chronic, and most constantly experience active lesions that persist for months. Nearly all respondents reported moderate daily pain, which for 46% of respondents, was poorly controlled with existing treatments; however, the input

did not detail which treatments the respondents were receiving or referring to. Most respondents (61%) expressed dissatisfaction with currently available treatment options, primarily due to the side effects, and the long wait times and challenging recovery processes for surgical treatment options. Respondents to the 2020 survey had tried, on average, 15 different medications, surgical procedures, home treatments, or lifestyle modifications to help manage their symptoms, but only a small proportion experienced significant improvement. Although there are prescription treatments that may benefit certain patients, less than 35% of respondents had accessed them, and many emphasized the high personal cost of wound care and treatment, which the input noted, suggests access and affordability challenges.

Improved access to affordable, safe, and effective treatments with better pain management and symptom relief were identified as a top priority for patients. Primary treatment goals highlighted by patients in the 2020 National Report survey submitted by the patient group included symptom control (90%), a complete cure (71%), and the ability to enjoy personal relationships (69%). Diagnostic delays were a significant issue for respondents, who noted that delays often result in worsened symptoms and progression to more advanced disease by the time an accurate diagnosis is received.

The patient group input included the experiences of 4 patients who had received bimekizumab for HS treatment. At least 2 began treatment through a clinical trial, while 1 accessed it through private insurance. Three of the 4 patients reported symptom improvement while receiving bimekizumab; however, 2 discontinued treatment due to side effects, particularly fatigue. One patient continues to receive the therapy, noting that they are “doing quite well on it.” The respondent who accessed bimekizumab through private insurance was receiving treatment for 1.5 years and reported a reduction in flare intensity, in particular, with fewer abscesses in affected areas.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts noted that current management options, adalimumab and secukinumab, can reduce pain and flares, and slow or halt disease progression. However, they noted that responses to these treatments vary and many patients eventually experience a treatment response plateau or loss. The experts indicated that while secukinumab was a useful addition to the treatment landscape, it is often underdosed and insufficient to achieve full disease control. Conversely, even when dose escalated, adalimumab demonstrates waning effectiveness over time or may induce anti-drug antibodies, according to the experts. The clinical experts indicated that some off-label therapies, including infliximab, show some efficacy in managing HS but are challenging to access as coverage requests are rarely, if ever, approved through special access programs. The experts also noted that off-label treatment options are also typically insufficient to fully control disease.

The clinical experts suggested that bimekizumab could be used as a first-line advanced therapeutic if patients experience treatment failure after trialling a 3-month course of anti-inflammatory antibiotics, and eligibility should align with the criteria for treatment with adalimumab and secukinumab. One expert suggested allowing patients to initiate bimekizumab treatment as long as they were currently undergoing a 3-month course of antibiotics, because for many moderate to severe cases of the disease, it is evident early

in this period that biologic therapy would be necessary afterwards. The experts noted that early intervention is a key factor in managing HS and saving tissue, by stopping tunnelling and scarring. The experts noted that some patients with HS that does not respond adequately to 1 biologic will experience treatment response with a different biologic, and therefore prior biologic treatment should not impact the patients' access to another option. The clinical experts indicated that patients with moderate to severe HS, or Hurley stage II to III, would be best suited for bimekizumab treatment, especially if they also have psoriasis. The experts indicated that there is currently no method of assessing whether patients' disease will respond better to anti-tumour necrosis factor (TNF) or anti-IL-17 therapy. However, some patients for whom anti-TNF therapy is not suitable (e.g., those with lupus, severe cardiovascular disease, recent malignancy, or demyelinating disease) may instead benefit from bimekizumab, according to the experts. Patients for whom bimekizumab is least suited are those with known IBD, recurrent and severe candidiasis, and a known hypersensitivity to the drug. The clinical experts noted that HS is most often diagnosed clinically, using Hurley staging, and is rarely misdiagnosed by dermatologists. While bedside imaging has been used by some providers, the experts noted that this method is not validated or accessible to all patients.

The experts noted that measures of assessing treatment response in clinical practice largely align with those in clinical trials. For objective outcomes, nodules and abscesses including number of lesions, are compared before and after starting therapy, ideally at least 3 to 6 months after initiation. Pain score reductions are sometimes recorded, although these are less often measured in practice. Key patient-reported outcomes indicating a positive treatment response are decreased pain and drainage, as well as reduction in flare frequency and intensity. One clinical expert indicated that patient-reported outcomes are often more representative of treatment response, as chronic scarring from lesions can preclude the ability to see lesion clearance. The clinical experts considered a clinically meaningful treatment response to be at least a 25% reduction in abscess and nodule count after 3 months and/or a 50% reduction by 6 months. The experts anticipated that disease improvement will be slow for most patients, as heavily inflammatory lesions subside slowly and lifestyle factors such as stress and dietary triggers may cause flares. The clinical experts indicated that bimekizumab discontinuation should be considered in the event of adverse reactions, minimal to no reduction in abscesses and nodules, and no decrease in pain within the first 3 to 6 months of treatment. The clinical experts agreed that bimekizumab treatment should be initiated and managed by dermatologists with a thorough understanding of HS to ensure proper use and monitoring of biologics and effective management of potential adverse events (AEs). The input received about whether it would be appropriate for other specialties to prescribe bimekizumab for and monitor treatment of patients with HS was mixed; however, general practitioners with dermatology expertise may be considered when access to a dermatologist may be an issue.

Clinician Group Input

One clinician group, the Atlantic Dermatology Specialist Group, submitted input for this review based on contributions from 4 clinicians. The Atlantic Dermatology Specialist Group comprises dermatology-certified physicians practising general dermatology who have extensive experience in managing various skin conditions, including HS. Information was gathered for this input submission by reviewing relevant published literature based on clinical disease experience.

Overall, clinician group input was consistent with input provided by the consulted clinical experts. Some of the feedback received varied slightly and are described herein. The clinician group noted that adalimumab and secukinumab achieve modest HS symptom improvement and often fail to improve permanent lesion scarring, and many patients continue to experience draining, painful, scarring lesions, or intolerable side effects. They also indicated additional treatment goals, including reducing the need for surgical intervention, preventing comorbidities, and enabling patients to return to the workforce. According to the clinician group, an “ideal” HS treatment would result in 90% to 100% of patients achieving Hidradenitis Suppurativa Clinical Response 50 (HiSCR50) (defined as $\geq 50\%$ reduction in abscess and inflammatory nodule [AN] count, with no increase in the number of abscesses and/or draining tunnels), with a large proportion achieving 90% to 100% reductions. Consistent with input provided by the experts consulted for this review, the clinician group anticipated that bimekizumab will be used in the first line, adding that it could be used as monotherapy or in combination with other therapies for maintenance and/or flares. The clinician group anticipated that bimekizumab would cause a shift in the current treatment paradigm, noting that they have found it to be more efficacious than current treatments in clinical practice. The clinician group also noted that bimekizumab is the first to be evaluated for and meet higher efficacy end points, such as Hidradenitis Suppurativa Clinical Response 90 (HiSCR90) (defined as $\geq 90\%$ reduction in AN count, with no increase in the number of abscesses and/or draining tunnels) and Hidradenitis Suppurativa Clinical Response 100 (HiSCR100) (defined as a 100% reduction in AN count, with no increase in the number of abscesses and/or draining tunnels). Both the clinical experts and the clinician group emphasized the importance of aligning bimekizumab initiation criteria with those of other biologic treatments and not requiring patients to first try other biologic options. They advised against the use of bimekizumab in individuals younger than 18 years or those who are pregnant or breastfeeding, or in combination with other biologics due to a lack of research. For patients with HS that is responding to therapy, the clinician group recommended reassessment every 12 months or as needed in the event of AEs or loss of response. They also noted that treatment discontinuation should be considered if no response is observed after 4 to 6 months or if intolerable AEs or pregnancy occur. While the experts and the clinician group agreed that bimekizumab should be initiated by practitioners with expertise in HS and biologic therapies, the clinician group added that prescription renewal could be performed by any practitioner able to assess disease severity and monitor treatment efficacy and AEs.

Drug Program Input

The drug programs identified issues related to relevant comparators, considerations for initiation, renewal, discontinuation and prescribing of therapy, and system and economic issues ([Table 4](#)).

Clinical Evidence

Systematic Review

Description of Studies

Two double-blind, placebo-controlled, randomized controlled trials (RCTs), the BE HEARD I (N = 505) and BE HEARD II (N = 509) trials, evaluated the efficacy and safety of bimekizumab versus placebo in adults (aged 18 years and older) with moderate to severe HS for at least 6 months before the baseline visit. All

patients had a history of inadequate response to systemic antibiotics used for treating HS. The primary objective was the same in both trials: to evaluate the efficacy of bimekizumab in patients with moderate to severe HS based on an HiSCR score reduction of 50% or greater (HiSCR50) at week 16. The secondary objectives were also identical: to evaluate the efficacy of bimekizumab on other measures of disease activity and the safety of bimekizumab in patients with moderate to severe HS. Secondary efficacy end points were also assessed at week 16, and the measures of disease activity included Hidradenitis Suppurativa Clinical Response 75 (HiSCR75), defined as at least a 75% reduction in AN count with no increase in the number of abscesses and/or draining tunnels, absolute change from baseline in Dermatology Life Quality Index (DLQI) total score, absolute change in skin pain score as per the Hidradenitis Suppurativa Symptom Daily Diary (HSSDD), and skin pain response based on a clinically meaningful change from baseline in the HSSDD. The BE HEARD II trial included 1 additional measure of disease activity as a secondary efficacy end point, which was the occurrence of a flare by week 16.

Both trials were completed in 3 study periods: an initial screening period; a 48-week treatment period; and a 20-week safety period for posttreatment follow-up. The treatment period comprised a double-blind, placebo-controlled initial treatment period (week 0 to 16), followed by a double-blind 32-week maintenance treatment period (week 16 to 48), during which all patients received bimekizumab. In both studies, patients were randomized (2:2:2:1) to receive either bimekizumab 320 mg every 2 weeks from week 0 to 48; bimekizumab 320 mg every 4 weeks from week 0 to 48; bimekizumab 320 mg every 2 weeks from week 0 to 16, and then bimekizumab 320 mg every 4 weeks from week 16 to 48; or placebo until week 16, and then bimekizumab 320 mg every 2 weeks from week 16 to 48.

The recommended dosing approved by Health Canada is bimekizumab 320 mg every 2 weeks for the first 16 weeks, followed by bimekizumab 320 mg every 4 weeks thereafter. Within each study, data were pooled for the 2 groups that received bimekizumab 320 mg every 2 weeks during the initial treatment period, which were formally compared to the placebo group at week 16. In addition, data from the 2 groups that switched regimens for the maintenance treatment period are presented as supporting evidence from week 16 to 48, which includes the group that switched from placebo (received during the initial treatment period) to bimekizumab every 2 weeks (during the maintenance treatment period), and the group that switched from bimekizumab every 2 weeks during the initial treatment period to every 4 weeks during the maintenance treatment period.

Across both trials, the mean age of patients ranged from 36.4 years (standard deviation [SD] = 12.4) in the placebo group in the BE HEARD I trial to 38.1 years (SD = 13.2) in the placebo group in the BE HEARD II trial. At baseline, most patients were diagnosed with Hurley stage II (derived) disease severity, ranging from 47.2% (34 of 72 patients) in the placebo group in the BE HEARD I trial to 60.8% in both the bimekizumab (177 of 291 patients) and placebo (45 of 74 patients) groups in the BE HEARD II trial. Mean disease duration ranged from 7.4 years in the bimekizumab group in the BE HEARD II trial to 11.5 years in the placebo group in the BE HEARD I trial. In the BE HEARD I trial, most patients in both groups were female (60.9% in the bimekizumab group and 61.1% in the placebo group), whereas in the BE HEARD II trial, 51.5% of the bimekizumab group was female versus 41.9% of the placebo group.

Efficacy Results

Input from patient groups, clinician groups, and clinical experts emphasized the need for new HS treatments that are safe and effective (i.e., reduce lesions or flares and pain) and that lead to disease remission. Some key goals highlighted by the experts consulted during the review of HS management in current practice included pain reduction, minimizing drainage, prevention of new lesions and flares, and slowing or halting disease progression. In consultation with the experts, the study outcomes assessed in this clinical review were determined to best represent these treatment goals and considered the most realistic to clinical practice; therefore, they were the focus of this review.

HiSCR50 Responder Rate

The primary efficacy end point in both trials was the proportion of patients who achieved HiSCR50 at week 16 (primary end point), defined as a greater than or equal to 50% reduction from baseline in total AN count, with no increase from baseline in the number of abscesses and/or draining tunnels.

BE HEARD I study: The HiSCR50 responder rate (adjusted for intercurrent events and missing information imputed) at week 16 was 44.8% (95% confidence interval [CI], 35.8% to 53.8%) in the pooled bimekizumab 320 mg every 2 weeks group versus 26.7% (95% CI, 15.0% to 38.4%) in the placebo group (odds ratio [OR] = 2.23; 97.5% CI, 1.16 to 4.31; $P = 0.006$ [tested at $\alpha = 0.025$]). The between-group difference was 18.15% (95% CI, 6.31% to 29.98%) in favour of bimekizumab.

BE HEARD II study: The HiSCR50 responder rate (adjusted for intercurrent events and missing information imputed) at week 16 was 50.3% (95% CI, 41.5% to 59.0%) in the pooled bimekizumab 320 mg every 2 weeks group versus 30.7% (95% CI, 18.6% to 42.7%) in the placebo group (OR = 2.29; 97.5% CI, 1.22 to 4.29; $P = 0.003$ [tested at $\alpha = 0.025$]). The between-group difference was 19.61% (95% CI, 7.50% to 31.72%) in favour of bimekizumab.

HiSCR50 responder rates at week 48 were exploratory outcomes in both studies. In the BE HEARD I trial, in the pooled bimekizumab 320 mg every 2 weeks followed by every 4 weeks group, responder rates were 40.2% (95% CI, 31.7% to 48.7%). In the BE HEARD II trial, responder rates at week 48 in the pooled bimekizumab 320 mg every 2 weeks followed by every 4 weeks group were 44.5% (95% CI, 36.0% to 53.0%).

HiSCR75 Responder Rate

HiSCR75 at week 16 was assessed as a ranked secondary outcome in the BE HEARD I and II trials.

BE HEARD I study: The HiSCR75 responder rate (adjusted for intercurrent events and missing information imputed) at week 16 was 35.7% (95% CI, 27.0% to 44.4%) in the pooled bimekizumab 320 mg every 2 weeks group versus 20.3% (95% CI, 9.4% to 31.2%) in the placebo group (OR = 2.18; 97.5% CI, 1.02 to 4.64; $P = 0.021$ [tested at $\alpha = 0.025$]). The between-group difference was 15.35% (95% CI, 3.71% to 27.00%) in favour of bimekizumab.

BE HEARD II study: The HiSCR75 responder rate (adjusted for intercurrent events and missing information imputed) at week 16 was 36.8% (95% CI, 28.4% to 45.2%) in the pooled bimekizumab 320 mg every 2

weeks group versus 16.3% (95% 6.8% to 25.7%) in the placebo group (OR = 3.01; 97.5% CI, 1.37 to 6.58; $P = 0.002$ [tested at $\alpha = 0.025$]). The between-group difference was 20.57% (95% CI, 9.90% to 31.26%) in favour of bimekizumab.

Responder rates for HiSCR75 up to week 48 were reported in both trials as exploratory end points.

BE HEARD I study: Responder rates at week 48 were 28.1% (95% CI, 20.2% to 35.9%) in the bimekizumab 320 mg every 2 weeks followed by every 4 weeks group and 26.6% (95% CI, 15.9% to 37.3%) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

BE HEARD II study: Responder rates at week 48 were 32.8% (95% CI, 24.8% to 40.8%) in the bimekizumab 320 mg every 2 weeks followed by every 4 weeks group and 48.5% (95% CI, 36.7% to 60.4%) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

Flare

A flare was defined as a minimum 25% increase in AN count, with an absolute increase greater than or equal to 2 AN counts relative to baseline. In the BE HEARD I trial, flare rate by week 16 was analyzed descriptively as a nonranked secondary end point; in the BE HEARD II trial, flare by week 16 was tested as a ranked secondary end point, but was not found to be significantly different, terminating hierarchical testing. In both trials, flare by week 48 was an exploratory outcome and only presented descriptively. The clinical experts noted that because the goal in real-world practice is to reduce flares over a longer time period, flare by week 48 was considered more clinically relevant.

BE HEARD I study: By week 16, 28.5% (95% CI, 23.2% to 33.9%) of patients in the pooled bimekizumab 320 mg every 2 weeks group reported a flare. By week 48, 55.9% (95% CI, 47.6% to 64.3%) of patients in the bimekizumab 320 mg every 2 weeks or every 4 weeks group reported a flare.

BE HEARD II study: By week 16, 28.8% (95% CI, 23.5% to 34.1%) of patients in the pooled bimekizumab 320 mg every 2 weeks group reported a flare compared with 28.0% (95% CI, 17.6% to 38.4%) of patients in the placebo group (OR = 1.050; 97.5% CI, 0.541 to 2.041; $P = 0.868$ [tested at $\alpha = 0.025$]). By week 48, 51.2% (95% CI, 42.9% to 59.4%) in the bimekizumab 320 mg every 2 weeks or every 4 weeks group reported a flare.

Change From Baseline in DLQI Total Score

Change from baseline in DLQI total score at week 16 was included as a ranked secondary outcome in both trials. A minimal important difference (MID) of 4 points was adopted by the sponsor as a clinically meaningful threshold, based on evidence from prior studies of other skin conditions (but not HS).

BE HEARD I study: The least squares (LS) mean change from baseline to week 16 was -5.21 (95% CI, -6.14 to -4.29) in the pooled bimekizumab 320 mg every 2 weeks group and -2.53 (95% CI, -4.07 to -0.996) in the placebo group. The between-group treatment difference was -2.68 (97.5% CI, -4.39 to -0.97; $P < 0.001$ [tested at $\alpha = 0.025$]), in favour of bimekizumab.

BE HEARD II study: The LS mean change from baseline was -4.69 (95% CI, -5.49 to -3.897) in the pooled bimekizumab 320 mg every 2 weeks group versus -2.38 (95% CI, -3.64 to -1.13) in the placebo group. The between-group difference was -2.31 (97.5% CI, -3.71 to -0.91). Statistical significance could not be interpreted due to a nonsignificant result in a prior step in the statistical testing procedure.

The change from baseline in DLQI total score was reported up to week 48 in both trials. In the bimekizumab every 2 weeks or every 4 weeks group, mean change from baseline at week 48 was -5.0 (standard error [SE] = 0.6) in the BE HEARD I trial and -5.4 (SE = 0.6) in the BE HEARD II trial. In the placebo followed by bimekizumab every 2 weeks group, mean change from baseline was -6.1 (SE = 1.2) in the BE HEARD I trial and -6.7 (SE = 0.8) in the BE HEARD II trial.

Change From Baseline in Hidradenitis Suppurativa Quality of Life Total Score

Change from baseline in the Hidradenitis Suppurativa Quality of Life (HiSQOL) total score up to week 48 was assessed as an exploratory outcome in both trials. A clinically meaningful change in HiSQOL was defined as a minimum 20-point reduction from baseline score.

BE HEARD I study: By week 16, the mean change from baseline in HiSQOL total score was -11.1 (SE = 1.1) in the pooled bimekizumab 320 mg every 2 weeks group and -5.2 (SE = 1.6) in the placebo group. By week 48, the mean change from baseline was -12.3 (SE = 1.3) in the bimekizumab 320 mg every 2 weeks followed by every 4 weeks group and -13.0 (SE = 2.2) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

BE HEARD II study: By week 16, the mean change from baseline in HiSQOL total score was -10.3 (SE = 1.0) in the pooled bimekizumab 320 mg every 2 weeks group and -5.8 (SE = 1.3) in the placebo group. By week 48, the mean change from baseline was -13.4 (SE = 1.2) in the bimekizumab 320 mg every 2 weeks followed by every 4 weeks group and -15.6 (SE = 1.6) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

Worst Skin Pain Responder Rate, Based on Clinically Meaningful Change in the HSSDD

The HSSDD is a patient-reported outcome that evaluates patient perception of the main HS symptoms over a 24-hour recall period. At week 16, the HSSDD worst skin pain responder rate was assessed as a ranked secondary outcome, based on a clinically meaningful change in the worst skin pain item among study participants who had a score of 3 or more at baseline. A clinically meaningful change in the HSSDD worst skin pain score was defined as a minimum 3-point reduction from baseline score, based on weekly averages.

BE HEARD I study: The adjusted responder rate was 35.4% (95% CI, 24.1% to 46.6%) in the pooled bimekizumab 320 mg every 2 weeks group versus 16.7% (95% CI, 3.6% to 29.8%) in the placebo group (OR = 2.76; 97.5% CI, 0.91 to 8.36; $P = 0.041$ [tested at $\alpha = 0.025$]). The between-group difference was 18.66% (95% CI, 3.32% to 33.99%) in favour of bimekizumab 320 mg every 2 weeks.

BE HEARD II study: The adjusted responder rate was 29.8% (95% CI, 18.9% to 40.7%) in the pooled bimekizumab 320 mg every 2 weeks group versus 10.2% (95% CI, 0.7% to 19.7%) in the placebo group (OR = 3.76; 97.5% CI, 1.189 to 11.867). The between-group difference was 19.57% (95% CI, 7.50% to

31.64%). Statistical significance could not be interpreted due to a prior nonsignificant result in the statistical testing hierarchy.

The HSSDD worst skin pain score response based on clinically meaningful change at week 48 was not assessed in either of the trials.

Harms Results

Harms data for the initial treatment period and overall treatment period are presented for both trials.

Initial Treatment Period

In the initial treatment period, 67.1% of patients in the bimekizumab 320 mg every 2 weeks group and 66.7% of patients in the placebo group reported at least 1 AE in the BE HEARD I trial compared to 64.5% of patients in the bimekizumab 320 mg every 2 weeks group and 56.8% in the placebo group in the BE HEARD II trial. The most frequently reported AEs ($\geq 5\%$ of patients) in the BE HEARD I trial in the bimekizumab 320 mg every 2 weeks group versus the placebo group were hidradenitis (6.6% versus 13.9%, respectively), back pain (2.4% versus 8.3%, respectively), and headache (7.7% versus 4.2%, respectively), and in the BE HEARD II trial, diarrhea (6.2% versus 8.1%, respectively), headache (6.2% versus 9.5%, respectively), and hidradenitis (8.6% versus 6.8%, respectively).

The proportion of serious adverse events (SAEs) reported in the pooled bimekizumab 320 mg every 2 weeks group was 2.1% in the BE HEARD I trial and 3.1% in the BE HEARD II trial. No SAEs were reported in the placebo group in either study. In the BE HEARD I trial, 3.5% of patients in the pooled bimekizumab 320 mg every 2 weeks group and 1.4% of patients in the placebo group discontinued study treatment due to AEs. No patients in the placebo group and 4.1% of patients in the bimekizumab 320 mg every 2 weeks group discontinued study treatment due to AEs in the BE HEARD II trial. There were no deaths reported in either study.

Oral candidiasis was a notable harm identified by the clinical experts consulted for this review. In the initial treatment period (the safety set, defined as the study participants who received at least 1 full or partial dose of the drug under investigation) of both the BE HEARD I and II trials, oral candidiasis was reported in 5.9% and 8.3%, respectively, of patients in the pooled bimekizumab 320 mg every 2 weeks groups. No oral candidiasis was reported in the placebo groups of either trial.

Overall Study Period

The recommended dosing approved by Health Canada is bimekizumab 320 mg every 2 weeks for the first 16 weeks of treatment, followed by bimekizumab 320 mg every 4 weeks thereafter. Therefore, the most relevant treatment arm in the maintenance treatment period (and the overall treatment period) is the bimekizumab 320 mg every 2 weeks or every 4 weeks group, and this is the focus of this harms summary.

In the overall treatment period (the initial and maintenance treatment periods), 85.5% of patients in the BE HEARD I trial and 87.7% of patients in the BE HEARD II trial reported at least 1 AE in the bimekizumab 320 mg every 2 weeks or every 4 weeks group. The AEs ($\geq 5\%$ of patients) most frequently reported by patients in this group in the BE HEARD I trial included diarrhea (8.3%), oral candidiasis (11.0%), folliculitis (7.6%),

and nasopharyngitis (8.3%). In the BE HEARD II trial, the most frequently reported AEs in the bimekizumab 320 mg every 2 weeks or every 4 weeks group included hidradenitis (21.2%), headache (9.6%), coronavirus infection (10.3%), and oral candidiasis (17.1%). The proportion of SAEs reported in the bimekizumab 320 mg every 2 weeks or every 4 weeks group was 5.5% in the BE HEARD I trial and 2.9% in the BE HEARD II trial. The incidence of AEs leading to study discontinuation in the bimekizumab 320 mg every 2 weeks or every 4 weeks group was 6.9% in the BE HEARD I trial and 6.8% in the BE HEARD II trial. There were no deaths reported in either study.

All the groups that received bimekizumab reported candida infections, most of which were oral candidiasis infections. In the BE HEARD I and BE HEARD II trials, 11.0% and 17.1%, respectively, of the bimekizumab 320 mg every 2 weeks or every 4 weeks groups reported oral candidiasis infection. Additional AEs of special interest included fungal infections, hypersensitivity reactions, opportunistic infections, and injection site reactions.

Critical Appraisal

Internal Validity

Two RCTs included in the systematic review were conducted using similar study and statistical methods. There were a few imbalances observed between the randomized treatment groups' baseline characteristics, but these were not expected to affect efficacy findings. The proportion of patients who discontinued the study was similar across groups in the initial treatment period, and low overall, as less than 10% of patients discontinued the study in any treatment group. Across all groups, the proportion of discontinuations in the maintenance treatment phase was higher than that in the initial treatment period. Nevertheless, the rates of study discontinuations in both treatment periods in the BE HEARD I and II trials were not considered to have a substantial impact on overall study findings. While there were many protocol deviations reported in both trials, most notably prohibited concomitant medication use, these deviations had minimal impact on the primary efficacy outcome.

The primary outcome (HiSCR50, tested at week 16) and key secondary outcomes in both trials and all time points were generally consistent with outcomes assessed in previous studies in populations with HS. The statistical methods used for the primary and secondary outcome analyses at week 16 in both trials were considered appropriate. After week 16, there was limited evidence of comparative efficacy of bimekizumab versus placebo for the key efficacy outcomes (HiSCR50, flares, HSSDD responder rates, and DLQI). Due to the lack of control for multiplicity for other secondary ranked outcomes and outcomes investigated at week 48, results for other secondary end points and outcomes at week 48 were considered exploratory. There were also concerns regarding significant amounts of missing data from patient-reported outcome questionnaires (DLQI and HSSDD) at week 16 and week 48.

Although patients and investigators were blinded to study treatments, the observed imbalance in reported AEs for patients receiving bimekizumab, notably oral candidiasis, may have increased the likelihood that patients and investigators were aware of treatment assignments. There is also a potential risk of assessment bias for the evaluation of subjective outcomes such as HiSCR and flares, which are physician assessed and prone to interobserver variation in the assessment of lesion counts. Similarly, it is possible that response bias

could have influenced patient-reported outcomes such as skin pain response and HRQoL (assessed using the DLQI), as these require subjective reporting by patients.

External Validity

The patient populations included in the trials were generally in line with patients seen in clinical practice in Canada with respect to age, sex, Hurley stage, duration of disease, and prior antibiotic use. The experts noted that, in their experience, the duration of HS and time to diagnosis were consistent with the experiences of patients in current practice. There were no major generalizability concerns regarding the baseline and demographic characteristics of the patients enrolled in the trials. Both trials were multinational studies with sites in Canada and many enrolled patients from Canada.

While the choice of placebo as a comparator in both studies was sufficient for assessing the efficacy and safety of bimekizumab in patients with HS, adalimumab would have been an ideal active comparator to evaluate relative effectiveness. The concomitant medications and procedures allowed during the trials aligned with clinical practice. There were no concerns with the rescue medications administered during the trials, as they align with drugs available in current practice.

The bimekizumab dosing and treatment schedule used in both trials aligns with the recommended dosing approved by Health Canada, which is bimekizumab 320 mg every 2 weeks for the first 16 weeks of treatment, followed by bimekizumab 320 mg every 4 weeks thereafter. While both studies included a group that received bimekizumab 320 mg every 4 weeks for the initial treatment period (first 16 weeks), efficacy and safety results from this group were not summarized for the purposes of this review, as the dosing schedule was outside of the approved indication. Although the 16-week duration of the initial treatment period was adequate to assess the clinical benefit of bimekizumab versus placebo in a clinical trial setting, the consulted clinical experts noted that a 6-month assessment is more applicable to clinical practice, as HS is often slow to respond to treatment. The experts noted that if after 16 weeks of treatment a patient does not show any response to treatment and/or shows disease worsening, they would consider discontinuing treatment. During the maintenance treatment period, patients received bimekizumab either every 2 weeks followed by every 4 weeks from week 16 to week 48. According to the consulted clinical experts, both dosage schedules (every 2 weeks and every 4 weeks) are applicable to clinical practice, as patients will likely require different dosage frequencies depending on disease stability. However, it is worth noting that the Health Canada–approved dosing recommendations for bimekizumab follow a fixed schedule and adjusting dosage frequency based on treatment response is not suggested.

The 48-week duration of treatment limits the generalizability of findings from both trials, as it does not provide sufficient long-term evidence of safety and efficacy of bimekizumab treatment. Given that HS is a chronic, lifelong condition with no cure, there is a need for comprehensive long-term evaluation. Extended follow-up with an appropriate active comparator is necessary to understand the long-term efficacy and safety of bimekizumab in patients with moderate to severe HS.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs 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 for informing the CDA-AMC expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.^{14,15}

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.

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 reference points for the certainty-of-evidence assessment for HiSCR50 response, flares, HSSDD worst skin pain, and DLQI total score were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review. The reference point for the certainty-of-evidence assessment for DLQI total score was set according to the presence or absence of an important effect based on the threshold identified by the sponsor and clinical experts. The reference points for the certainty-of-evidence assessment for notable harms were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts.

For the GRADE assessments, findings from the BE HEARD I and BE HEARD II studies were considered together and summarized narratively per outcome because these studies were similar in population, interventions, design, and outcome measures.

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 clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Proportion of patients who achieved HiSCR50 by week 16
- Proportion of patients who experienced a flare by week 48
- Proportion of patients who reported at least a 3-point reduction in HSSDD worst skin pain score by week 16
- Change from baseline in the DLQI total score by week 16
- Proportion of patients with 1 or more SAEs by week 16
- Proportion of patients who experienced oral candidiasis by week 16

Results of GRADE Assessments

[Table 2](#) presents the GRADE summary of findings for bimekizumab 320 mg every 2 weeks versus placebo.

Table 2: Summary of Findings for Bimekizumab vs. Placebo for Patients With HS

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Response to treatment and disease severity				
HiSCR50 response rate: The proportion of patients with $\geq 50\%$ reduction from baseline in total AN count, with no increase from baseline in number of abscesses or draining tunnels (95% CI) Follow-up: 16 weeks	726 (2 RCTs)	BE HEARD I: - Bimekizumab: 448 per 1,000 (358 to 538) - Placebo: 267 per 1,000 (150 to 384) - Difference: 182 more per 1,000 (63 more to 300 more per 1,000) BE HEARD II: - Bimekizumab: 503 per 1,000 (415 to 590) - Placebo: 307 per 1,000 (186 to 427) - Difference: 196 more per 1,000 (75 more to 317 more per 1,000)	Moderate ^a	Bimekizumab 320 mg q.2.w. likely results in an increase in the proportion of patients with HiSCR50 response when compared with placebo.
Disease worsening				
Flare: The proportion of patients who experienced a flare, defined as $\geq 25\%$ increase in AN count, with an absolute increase ≥ 2 AN counts relative to baseline (95% CI) Follow-up: 48 weeks	433 (2 RCTs)	BE HEARD I: - Bimekizumab q.2.w. followed by bimekizumab q.4.w.: [REDACTED] - Difference: NR BE HEARD II: - Bimekizumab q.2.w. followed by bimekizumab q.4.w.: [REDACTED] - Difference: NR	Very low ^b	The evidence is very uncertain about the effect of bimekizumab (320 mg q.2.w. to week 16, followed by q.4.w. from week 16 to 48) on flare rate when compared with placebo or an alternate dose of bimekizumab.
HRQoL				
DLQI total score (0 [best] to 30 [worst]), absolute LS mean change from baseline (97.5% CI) Follow-up: 16 weeks	646 (2 RCTs)	BE HEARD I: - Bimekizumab: -5.214 less (-6.139 less to -4.290 less) - Placebo: -2.532 less (-4.069 less to -0.996 less) - Difference: -2.682 less (-4.394 less to -0.970 less)	Moderate ^c	Bimekizumab 320 mg q.2.w. likely results in little to no clinically meaningful difference in DLQI total score mean change from baseline when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		BE HEARD II: • Bimekizumab: -4.692 less [-5.486 less to -3.897 less] • Placebo: -2.382 less [-3.636 less to -1.128 less] • Difference: -2.309 less (-3.705 less to -0.914 less)		
Symptoms				
Worst skin pain responder rate: Based on a clinically meaningful within-patient change among patients with a score of ≥ 3 at baseline in HSSDD (95% CI) Follow-up: 16 weeks	494 (2 RCTs)	BE HEARD I: • Bimekizumab: 354 more per 1,000 (241 more to 466 more) • Placebo: 167 more per 1,000 (36 more to 298 more) • Difference: 187 more per 1,000 (33 more to 340 more per 1,000) BE HEARD II: • Bimekizumab: 298 more per 1,000 (189 more to 407 more per 1,000) • Placebo: 102 more per 1,000 (7 more to 197 more per 1,000) • Difference: 196 more per 1,000 (75 more to 316 more per 1,000)	Low ^d	Bimekizumab 320 mg q.2.w. may result in little to no difference in worst skin pain response rate (measured using HSSDD score) when compared with placebo.
Harms				
SAE n (95% CI) Follow-up: 16 weeks	722 (2 RCTs)	BE HEARD I: • Bimekizumab: 21 per 1,000 (NR) • Placebo: 0 per 1,000 (NR) • Difference: 21 per 1,000 (4 more to 38 more per 1,000) BE HEARD II: • Bimekizumab: 31 per 1,000 (NR) • Placebo: 0 per 1,000 (NR) • Difference: 31 per 1,000	Moderate ^e	Bimekizumab 320 mg q.2.w. likely results in an increase in the proportion of patients with ≥ 1 SAEs when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		(11 more to 51 more per 1,000)		
Oral candidiasis n (95% CI) Follow-up: 16 weeks	722 (2 RCTs)	BE HEARD I: • Bimekizumab: 59 per 1,000 (NR) • Placebo: 0 (NR) • Difference: 59 more per 1,000 (32 more to 87 more per 1,000) BE HEARD II: • Bimekizumab: 83 per 1,000 (NR) • Placebo: 0 (NR) • Difference: 83 more per 1,000 (51 more to 115 more per 1,000)	Moderate ^e	Bimekizumab 320 mg q.2.w. weeks likely results in an increase in the proportion of patients with oral candidiasis relative to placebo.

AN = abscess and inflammatory nodule; CI = confidence interval; DLQI = Dermatology Life Quality Index; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HS = hidradenitis suppurativa; HSSDD = Hidradenitis Suppurativa Symptom Daily Diary; HRQoL = health-related quality of life; LS = least squares; MID = minimal important difference; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; NR = not reported; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus.

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

^aBased on clinical expert input, a threshold for a clinically important between-group difference was 100 per 1,000 for the proportion of patients with HiSCR50 response. Rated down 1 level for imprecision. The 95% CI interval for difference between groups includes the possibility of no difference.

^bAll patients received bimekizumab from week 16 to week 48, and therefore there is no longer a comparative analysis to a relevant comparator (or placebo) beyond 16 weeks, i.e., for the assessment at week 48. In the absence of a comparator group, conclusions about efficacy relative to any comparator cannot be drawn and the certainty of evidence started at very low and could not be rated up.

^cRated down 1 level for serious imprecision. The MID of 4 points for the DLQI was selected as the threshold for a clinically important between-group difference based on the literature and clinical expert input. (The 97.5% CI for between-group difference in the BE HEARD I trial included the potential for important benefit.)

^dRated down 1 level for serious imprecision. An MID of 250 per 1,000 (i.e., 25%) was selected as a threshold for a clinically meaningful important between-group difference based on clinical expert input. Rated down 1 level for serious study limitations, i.e., risk of bias due to missing data.

^eIn the absence of a threshold for clinical importance, the null was used. Rated down 1 level for indirectness. The follow-up duration was limited to 16 weeks, which may be insufficient to detect uncommon SAEs or those that may develop over time.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Patients who had completed the maintenance treatment period of the BE HEARD I and II trials were eligible to enrol in a separate open-label, noncontrolled, extension trial, the BE HEARD EXT (NCT04901195) trial. The objective of the extension trial is to evaluate 2 bimekizumab dosing regimens (320 mg every 2 weeks and 320 mg every 4 weeks). This study was ongoing at the time of submission and was not submitted for this review.

Indirect Evidence

Description of Studies

The sponsor submitted indirect evidence in the form of a network meta-analysis (NMA) and a matching-adjusted indirect comparison (MAIC).

For outcomes reported between weeks 12 to 16, NMAs were conducted by the sponsor. Two NMA networks that compared bimekizumab to secukinumab and adalimumab were analyzed. One network included a mixed population of patients who were biologic experienced and biologic naive (9 trials, N = 3,129), of whom approximately 20% had experience with biologics. The sponsor also analyzed a network consisting exclusively of patients who had experience with biologics (4 trials, N = not reported).

An unanchored MAIC was used to assess relative efficacy of bimekizumab with secukinumab and adalimumab after 48 to 52 weeks of treatment because it was not possible to form a connected network within the NMA for these time points.

Efficacy Results

Network Meta-Analysis

Mixed Biologic-Experienced and Biologic-Naive Population

For the binary outcomes, the results of the HiSCR50 analysis favoured bimekizumab every 2 weeks over secukinumab every 2 weeks (OR = 1.70; 95% credible interval [CrI], 1.16 to 2.45) and over secukinumab every 4 weeks (OR = 1.69; 95% CrI, 1.14 to 2.43), for the fixed-effects models. The results observed in the random-effects model had 95% CrIs that crossed the null for the comparison of bimekizumab every 2 weeks versus secukinumab every 2 weeks () and versus secukinumab every 4 weeks ().

The results of the HiSCR50 analysis for the comparison of bimekizumab every 2 weeks versus adalimumab every week did not favour either treatment, with 95% CrIs that crossed the null for the fixed-effects model (OR = 1.30; 95% CrI, 0.85 to 1.92) and the random-effects model ().

The results of the HiSCR75 analysis favoured bimekizumab every 2 weeks over secukinumab every 2 weeks (OR = 2.02; 95% CrI, 1.38 to 3.20) and over secukinumab every 4 weeks (OR = 1.85; 95% CrI, 1.26 to 2.90), for the fixed-effects models. The results of the HiSCR75 analysis favoured bimekizumab every 2 weeks over secukinumab every 2 weeks () and over secukinumab every 4 weeks (), for the random-effects models.

The results of the HiSCR75 analysis also favoured bimekizumab every 2 weeks over adalimumab every week (OR = 1.60; 95% CrI, 1.10 to 2.60) for the fixed-effects model. In the random-effects model, the results of the HiSCR75 analysis for the comparison of bimekizumab every 2 weeks versus adalimumab every week did not favour either treatment, with 95% CrIs that crossed the null ().

The results for the random-effects models show greater imprecision and some of the results that favoured bimekizumab in the fixed-effects models do not show the same degree of benefit in the random-effects models (the CrI crossed the null). The sponsor did not provide adequate justification for relying solely on the results of the fixed-effects models, and therefore, the random-effects models need to be considered in the evaluation of the relative efficacy of bimekizumab.

Biologic-Experienced Subgroup

Matching-Adjusted Indirect Comparison

The results of the MAIC favour bimekizumab every 2 weeks over secukinumab every 2 weeks and over secukinumab every 4 weeks for HiSCR50, HiSCR75, HiSCR90, and DLQI minimal clinically important difference (MCID) 5-point reduction. The 95% CIs do not cross the null for any of these comparisons.

The results of the MAIC favour bimekizumab every 2 weeks over adalimumab for HiSCR50 but not for HiSCR75 and HiSCR90. The 95% CIs do not cross the null for the HiSCR50 results, but do for the HiSCR75 and the HiSCR90 results.

Network Meta-Analysis

The presentation of 2 networks was reasonable. One network contained mixed biologic-experienced and biologic-naïve populations (9 trials, N = 3,129). Across all 3 treatment arms in the BE HEARD trials, 191 of 1,014 patients (18.8%) had experience with biologics. Across the treatment arms in the SUNRISE and SUNSHINE trials, 255 of 1,084 patients (23.5%) had experience with biologics. The lack of a network with patients who had no experience with biologics is a weakness of the analyses, as there were no relative efficacy estimates for this population. The other network contained biologic-experienced populations.

In the mixed biologic-experienced and biologic-naïve population, several results demonstrated differences favouring bimekizumab over secukinumab and adalimumab, but these findings were not consistent across all outcomes. There were no differences observed for bimekizumab versus comparators for Dermatology Life Quality Index. The reason for the incongruity in the dermatology-related quality of life results, compared to the HiSCR, is not clear. The results in the biologic-experienced network had wide CrIs and only data from 2

outcomes were presented, and therefore there was no clearly demonstrated advantage of bimekizumab over secukinumab in this subgroup.

There were fewer results in which bimekizumab was favoured over adalimumab, compared to the number of results in which bimekizumab was favoured over secukinumab.

Matching-Adjusted Indirect Comparison

The sponsor performed an unanchored MAIC because of the lack of a connected treatment network for the 48- to 52-week time points. This was an adequate justification for performing the MAIC. The selection of comparators was reasonable, according to the clinical experts consulted for this review. The MAIC analyses suggested that there were differences favouring bimekizumab compared to secukinumab, which were seen across several outcomes. However, the results for bimekizumab versus adalimumab across the outcomes were not as consistent as the comparisons with secukinumab.

The sponsor's list of 16 matching variables was reasonable, but there may have been important differences between the studies included in the MAIC that were not accounted for. In addition, some of the matching variable data were not available for all studies and all outcomes, therefore not all analyses applied all matching variables. Study design differences cannot be adjusted for in the MAIC weighting procedures.

The sponsor did attempt to use prior biologic exposure as a matching variable, but there were no analyses in the MAIC that analyzed an exclusively biologic-naïve population or an exclusively biologic-experienced population.

In the MAIC analyses, the effective sample size for the bimekizumab group was reduced to 70% from 77% for the comparison to secukinumab, and to 46% from 47% for the comparison to adalimumab.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps were submitted by the sponsor.

Conclusions

Collectively, the evidence from the BE HEARD I (N = 505) and BE HEARD II (N = 509) studies demonstrated that 16 weeks of treatment with bimekizumab 320 mg every 2 weeks likely results in a clinically meaningful improvement in HS inflammatory lesions (as measured by HiSCR50 response) when compared to placebo, in patients aged 18 years and older with moderate to severe HS. Improving quality of life and pain were identified by clinicians and patients as important treatment goals for patients living with HS, and the change from baseline to week 16 in the DLQI total score and worst skin pain responder rate (measured with HSSDD) were included as key secondary outcomes in the BE HEARD trials. The reported between-group differences were assessed with low certainty suggesting that bimekizumab 320 mg every 2 weeks may result in little to no clinically meaningful difference, when compared with placebo. Of note, the assessment of HRQoL based on the DLQI was limited by an MID that is not specific to HS and an assessment at 16 weeks that is likely too soon to expect a clinically meaningful improvement. There was also a high level of uncertainty as to whether bimekizumab 320 mg reduces the proportion of patients experiencing a flare by week 48 due to a lack of comparator during the maintenance treatment period. The results from the sponsor-conducted

NMA (weeks 12 to 16) and MAIC (weeks 48 to 52) suggested that bimekizumab may have advantages over secukinumab in treating HS inflammatory lesions (as measured by HiSCR50 response) in patients with HS who are biologic naive and biologic experienced, but methodological limitations and inconsistent results across models make the magnitude of benefit uncertain. Indirect comparisons provided no clear indication of a difference between bimekizumab and adalimumab. No new concerns regarding the harms of bimekizumab were identified based on the harms data observed with treatment for up to 48 weeks across the BE HEARD trials. The proportions of SAEs and of patients who discontinued treatment due to AEs were low, and no deaths were reported. Notable harms, such as oral candidiasis, were aligned with expectations for bimekizumab and considered manageable in clinical practice with no meaningful consequences. In the absence of a comparator group for the 48-week follow-up time point, it is not possible to draw definitive conclusions about the long-term efficacy or harms of bimekizumab versus any comparator, including placebo.

Introduction

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of bimekizumab (320 mg, subcutaneous injection) for adult patients with moderate to severe HS.

Disease Background

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following has been summarized and validated by the review team.

HS is a chronic, systemic, and debilitating inflammatory skin disease resulting from hair follicle occlusion, which results in a cycle of chronic inflammation, abscess formation, and inflamed nodules with draining tunnels and scarring.^{1,2} The disease often presents with tender subcutaneous nodules that develop in areas that are rich in apocrine glands, such as the axillary, groin, perianal, perineal, and inframammary locations.^{1,2} HS is thought to involve a combination of factors including immune and endocrine dysregulation, genetics, and bacterial infection.¹⁸⁻²¹ Symptoms of HS include pain, itch, skin damage, infection, odorous secretions, and physical or movement limitations, which can interfere with physical functioning, activities of daily living, work, and productivity.³⁻⁶ These symptoms can also substantially impact mental well-being, resulting in an increased risk of depression and anxiety, feelings of social isolation, decreased relationship satisfaction, and sexual dysfunction.^{3,7} HS is also associated with various comorbidities, including psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, IBD, polycystic ovarian syndrome, diabetes mellitus, thyroid disease, obesity, metabolic syndrome, acne, and pyoderma gangrenosum.^{8,9}

The prevalence of HS in Canada is estimated to be up to 3.8% of the general population, based on a 2016 survey.^{8,10} Of patients newly diagnosed with HS, 55% had mild HS and 45% had moderate to severe HS upon diagnosis, according to a single-centre chart review conducted in Canada.¹¹ Most patients with HS reported symptom onset during early adulthood, that is, in either late adolescence or during their twenties.¹ However, delayed diagnosis is common and the average time to diagnosis with HS is approximately 7 years

in Canada.⁶ Key risk factors for developing HS include biological sex, race, tobacco use, and obesity.²² HS disproportionately affects females, who have approximately 3 times the risk of developing the condition compared to males.^{22,23} In the US, Black patients have been shown to experience HS at a prevalence 2 to 3 times greater than white patients, often presenting with more severe disease.²⁴⁻²⁶ A 2024 meta-analysis found that tobacco use increases the risk of developing HS 3-fold and obesity 2.5-fold, and that the presence of these factors is linked to increased disease severity in affected individuals.²²

The diagnosis of HS is based on clinical presentation, without the use of any biological or pathological tests for diagnosis.^{3,9} The Dessau criteria are used to diagnose HS by characterizing recurrent, painful, or suppurating nodules that are present on 2 or more occasions within 6 months.^{8,9} In general, diagnosis of HS is based on 3 diagnostic criteria: lesion morphology (e.g., nodules, abscesses, or fistulas), distribution of lesions (e.g., axillary, inframammary, or perineal), and chronicity and recurrence (e.g., whether more than 2 lesions are present during a time period of 6 months or longer).⁸ Imaging may be used to confirm diagnosis and staging of HS; skin ultrasonography and MRI can detect specific features of HS.^{9,27,28} HS severity is evaluated using the Hurley staging system, based on the extent of inflammatory lesions, skin tunnels, and scarring.²⁹⁻³¹ Disease severity is classified into 3 groups: Hurley stage I (mild disease typically presenting as inflammatory nodules or abscess formation without sinus tracts and scarring); Hurley stage II (moderate disease typically presenting as recurrent abscesses and nodules with sinus tract formation or scarring either as single or multiple widely separated lesions); and Hurley stage III (severe and refractory disease typically presenting as diffuse or near-diffuse involvement with multiple interconnected sinus tracts, scarring, and abscesses across an entire area).

Standards of Therapy

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following has been summarized and validated by the review team.

The Canadian guidelines for the treatment and management of HS recommend personalizing treatments based on each patient's needs and treatment optimization according to disease stage (i.e., mild, moderate, or severe according to the Hurley system) for the management of HS.⁸ Topical therapies (e.g., skin cleansers, resorcinol, and antibiotics) may be used as adjuncts and may be effective in managing mild cases of HS; however, conventional systemic treatments (e.g., oral antibiotics, oral retinoids, oral contraceptives, or spironolactone) should be considered for patients with mild HS that is refractory to topical therapies.⁸ In cases of disease with suboptimal or inadequate response to conventional systemic treatments, patients with moderate to severe HS (Hurley stage II or III) may receive biologic therapy; for severe HS, early initiation of biologic therapy is recommended.⁸ Adalimumab and secukinumab are currently approved for treatment of HS in Canada. Bimekizumab, if reimbursed, will be a first-line biologic treatment option alongside adalimumab and secukinumab for patients with moderate to severe HS with an inadequate response to conventional therapy. The Canadian guidelines also recommend off-label infliximab as a second-line biologic, with off-label ustekinumab or off-label anakinra as third-line biologic options for treating HS.⁸

In addition to medical treatments, patients may concurrently undergo laser, procedural, and/or surgical treatments, which generally increase in invasiveness with HS severity.^{8,12,13} Laser hair removal may

be considered across the spectrum of HS, although its cost can be a barrier.⁸ Deroofing (curettage or electrosurgical removal of the “roof” of an abscess or sinus tract) may be considered alongside medical treatments for individual recurrent lesions as this may help prevent further recurrence in moderate to severe cases.⁸ In cases of extensive severe HS, wide local excision may be necessary to achieve disease control, followed by plastic surgery to address the excised area.⁸ While these techniques may be effective, they are associated with prolonged recovery times, recurrence, and complications.^{12,13} Moreover, surgical techniques are typically combined with medical treatment for optimal management,^{8,32,33} which suggests that the availability and reimbursement of better biologic treatments would benefit patients regardless of the strengths or limitations of surgical management.

Drug Under Review

Key characteristics of bimekizumab are summarized in [Table 3](#), with the characteristics of other treatments available for HS.

Bimekizumab is a humanized IgG1-k monoclonal antibody with 2 identical antigen-binding regions that target IL-17A, IL-17F, and IL-17A/F cytokines, blocking their interaction with the IL-17RA/IL-17RC receptor complex. Levels of IL-17A and IL-17F are elevated in lesional HS tissue, and dual neutralization of these cytokines results in suppressed expression of inflammation-related genes.

Bimekizumab is administered as a subcutaneous injection. The recommended dose of Bimzelx for adult patients with HS is 320 mg (given as 2 subcutaneous injections of 160 mg or 1 subcutaneous injection of 320 mg) every 2 weeks up to week 16 and every 4 weeks thereafter. Bimekizumab was reviewed and approved by Health Canada for the treatment of adult patients with moderate to severe HS with an inadequate response to conventional systemic therapy. Bimekizumab was approved in the US for the treatment of adults with moderate to severe HS and in the European Union for the treatment of active moderate-to-severe HS (acne inversa) in adults with an inadequate response to conventional systemic HS therapy.

The sponsor has submitted a deviation request for the reimbursement of bimekizumab in adult patients with moderate to severe HS with an inadequate response to conventional systemic therapy. This deviation request was accepted by CDA-AMC, and the focus of this review is the population requested for reimbursement.

Table 3: Key Characteristics of Bimekizumab, Secukinumab, and Adalimumab

Characteristic	Bimekizumab	Secukinumab	Adalimumab
Mechanism of action	Human IgG1-k monoclonal antibody that targets IL-17A, IL-17F, and IL-17A/F cytokines, blocking their interaction with the IL-17RA/IL-17RC receptor complex and suppressing expression of inflammation-related genes	Human IgG1-k monoclonal antibody that targets IL-17A, inhibiting its interaction with IL-17 receptors, thus inhibiting the release of cytokines and chemokines that promote inflammation	Recombinant human IgG1 monoclonal antibody that binds with high affinity and specificity to soluble TNF alpha but not lymphotoxin (TNF beta)

Characteristic	Bimekizumab	Secukinumab	Adalimumab
Indication^a	For the treatment of adult patients with moderate to severe HS with an inadequate response to conventional systemic therapy	For the treatment of adult patients with moderate to severe HS (acne inversa) who have responded inadequately to conventional systemic HS therapy	Treatment of active moderate-to-severe HS in adult and adolescent patients (12 years to 17 years weighing ≥ 30 kg) who have not responded to conventional therapy (including systemic antibiotics)
Route of administration	SC	SC	SC
Recommended dose	- From week 0 to 16, 320 mg (2 injections of 160 mg each) every 2 weeks - After week 16, 320 mg (2 injections of 160 mg each) every 4 weeks	Initial dose: 300 mg weekly through weeks 0 to 4 (either as a single injection or 2 injections of 150 mg) Maintenance dose: 300 mg monthly - For patients with body weight ≥ 90 kg, dose can be increased to 300 mg every 2 weeks	Initial dose: 80 mg at week 0 Maintenance dose: 40 mg every other week, starting at week 1 - If inadequate response, dose can be increased to 40 mg weekly
Serious adverse effects or safety issues	- Potential increase in infection risk - New onset and exacerbation of inflammatory bowel disease - Hypersensitivity reactions	- Potential increase in infection risk - New onset and exacerbation of inflammatory bowel disease	- Potential increase in risk of hepatosplenic T-cell lymphoma (rare, postmarket) - Serious infections - Pediatric malignancy (i.e., lymphoma)
Other	- Patients should be evaluated for TB infection before initiating treatment - Completion of all age-appropriate immunizations should be considered before initiating treatment	- Patients should be evaluated for TB infection before initiating treatment - Completion of all age-appropriate immunizations should be considered before initiating treatment	—

SC = subcutaneous; TB = tuberculosis; TNF = tumour necrosis factor.

^aHealth Canada–approved indication.

Sources: Bimekizumab Product Monograph;³⁴ Secukinumab Product Monograph;³⁵ Adalimumab Product Monograph.³⁶

Perspectives of Patients, Clinicians, and Drug Programs

The full patient and clinician group submissions received are available in the consolidated patient and clinician group input document for this review on the project website.

Patient Group Input

This section was prepared by the review team based on the input provided by patient groups.

CSPA and the HS Support Group collaboratively provided input for this review. CSPA is a national charity organization that aims to improve the health and well-being of people in Canada affected by skin, hair, and nail conditions through collaboration, advocacy, and education. The HS Support Group provides a safe space for individuals with HS to connect, share experiences, and learn about the condition. Information was gathered for this input submission through patient responses from 3 surveys: the CSPA's *Scarred for Life: 2020 Update. A National Report of Patients' Experiences Living with Hidradenitis Suppurativa*, the Health Policy Partnership's 2024 *Call to Action: Improving the Lives of People With Hidradenitis Suppurativa (HS) in Canada*, and a patient survey hosted by the patient groups from March 28, 2023, to May 23, 2023. The 2020 survey gathered responses from 537 individuals with HS, of whom 14% were from Canada, 12% from the UK, and 50% from the US. There was representation from across Canada, with most respondents from Ontario (41%) and Alberta (18%). In total, 15 responses were received from the 2023 survey, with all respondents from Canada and the majority from Ontario (47%) and Alberta (27%). The HS Support Group also requested, via a post in a Facebook group for Canadians with HS, that individuals who have received bimekizumab describe their experiences; 4 patients with relevant experience submitted responses.

Overall, survey respondents indicated that HS has a profoundly negative impact on their mental and physical health, social interactions, ability to carry out activities of daily living, intimacy, and work performance. In addition, patients highlighted specific concerns such as body odour, clothing stains, and the unpredictable nature of disease flares. All the respondents to the 2023 survey noted that their HS lesions are chronic, and most constantly experience active lesions that persist for months. Nearly all respondents reported moderate daily pain, which for 46% of respondents, was poorly controlled with existing treatments; however, the input did not detail which treatments the respondents were receiving or referring to. Most respondents (61%) expressed dissatisfaction with currently available treatment options, primarily due to the side effects, and the long wait times and challenging recovery processes from surgical options. Respondents to the 2020 survey had tried, on average, 15 different medications, surgical procedures, home treatments, or lifestyle modifications to help manage symptoms, but only a small proportion experienced significant improvement. Although there are prescription treatments that may benefit certain patients, less than 35% of respondents had accessed them and many emphasized the high personal cost of wound care and treatment, which the input noted, suggests access and affordability challenges.

Improved access to affordable, safe, and effective treatments with better pain management and symptom relief were identified as a top priority for patients. Primary treatment goals highlighted by patients in the 2020 National Report survey included symptom control (90%), curing disease completely (71%), and the ability to enjoy personal relationships (69%). Diagnostic delays were a significant issue for respondents, who noted that delays often result in worsened symptoms and progression to more advanced disease by the time an accurate diagnosis is received.

The patient group input included the experiences of 4 patients who had received bimekizumab treatment for HS. At least 2 began treatment through a clinical trial, while 1 accessed it through private insurance. Three

of the 4 patients reported symptom improvement while receiving bimekizumab; however, 2 discontinued treatment due to side effects, particularly fatigue. One patient continues to receive the therapy, noting that they are “doing quite well on it.” The respondent who accessed bimekizumab through private insurance was receiving treatment for 1.5 years and reported a reduction in flare intensity, in particular, with fewer abscesses in affected areas.

Clinician Input

Input From Clinical Experts Consulted for This Review

All CDA-AMC review teams include at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of HS.

Unmet Needs

The clinical experts consulted for this review noted that the current HS management options, adalimumab and secukinumab, can reduce pain and flares and slow or halt disease progression. However, the experts noted that responses to these treatments vary and many patients eventually experience a treatment response plateau or loss. The experts indicated that while secukinumab was a useful addition to the treatment landscape, it is often underdosed and insufficient to achieve full disease control. Conversely, even when dose escalated, adalimumab demonstrates waning effectiveness over time or may induce anti-drug antibodies, according to the experts. The experts reported that some off-label therapies, including infliximab, have shown efficacy in managing HS but they are challenging to access as coverage requests are rarely approved through special access programs. These off-label treatment options are also typically insufficient to fully control the disease.

Place in Therapy

The clinical experts suggested that bimekizumab could be used as a first-line advanced therapeutic if patients experience treatment failure after trialling a 3-month course of anti-inflammatory antibiotics, and eligibility should align with the criteria for treatment with adalimumab and secukinumab. One expert suggested allowing patients to initiate bimekizumab treatment as long as they were currently undergoing a 3-month course of antibiotics, because for many moderate to severe cases of the disease, it is evident early in this period that biologic therapy would be necessary afterwards. The experts noted that early intervention is a key factor in managing HS and saving tissue, by stopping tunnelling and scarring. The experts noted that some patients with HS that does not respond adequately to 1 biologic will experience treatment response with a different biologic, and therefore prior biologic treatment should not impact the patients' access to another option.

Patient Population

The clinical experts agreed that patients with moderate to severe HS, or Hurley stage II to III, would benefit from bimekizumab, especially if they also have psoriasis. The experts indicated that there is currently no method of assessing whether patients' disease will respond better to anti-TNF or anti-IL-17 therapy. However, some patients who are not suitable for anti-TNF therapy (e.g., those with lupus, severe cardiovascular disease, recent malignancy, or demyelinating disease) would be more suited to bimekizumab, according to the experts. Patients for whom bimekizumab is least suited are those with known IBD, recurrent and severe candidiasis, and a hypersensitivity to the drug. The clinical experts noted that HS is most often diagnosed clinically, using Hurley staging, and is rarely misdiagnosed by dermatologists. While bedside imaging has been used by some providers, the experts noted that this method is not validated or accessible to all patients.

Assessing the Response to Treatment

The experts noted that measures of assessing treatment response in clinical practice largely align with those in clinical trials. For objective outcomes, nodules and abscesses, including number of lesions, are compared before and after starting therapy, ideally at least 3 to 6 months after initiation. Pain score reductions are sometimes recorded, although this is less often measured in practice. Key patient-reported outcomes indicating a positive treatment response are decreased pain and drainage, as well as reduction in flare frequency and intensity. One clinical expert indicated that patient-reported outcomes are often more representative of treatment response, as chronic scarring from lesions can preclude the ability to see lesion clearance. The clinical experts considered a clinically meaningful treatment response to be at least a 25% reduction in abscess and nodule count after 3 months and/or a 50% reduction by 6 months. The experts anticipated that disease improvement will be slow for most patients, as heavily inflammatory lesions subside slowly and lifestyle factors such as stress and dietary triggers may cause flares.

Discontinuing Treatment

The clinical experts indicated that bimekizumab discontinuation should be considered in the event of adverse reactions, minimal to no reduction in abscesses and nodules, and no decrease in pain within the first 3 to 6 months of treatment.

Prescribing Considerations

The clinical experts agreed that bimekizumab treatment should be initiated and managed by dermatologists with a thorough understanding of HS to ensure proper use and monitoring of biologics and effective management of potential AEs; however, there was no consensus as to whether physicians with other specialties, including general practitioners with dermatology expertise, could prescribe and monitor bimekizumab treatment.

Clinician Group Input

This section was prepared by the review team based on the input provided by clinician groups.

One clinician group, the Atlantic Dermatology Specialist Group, submitted input for this review based on contributions from 4 clinicians. The Atlantic Dermatology Specialist Group comprises dermatology-certified

physicians practising general dermatology who have extensive experience in managing various skin conditions, including HS. Information was gathered for this input submission by reviewing relevant published literature and based on clinical disease experience.

According to the clinician group, the current approach to HS treatment includes both medical and surgical management to clear lesions, relieve symptoms, and prevent progression. Consistent with input provided by the experts consulted for this review, the clinician group noted that adalimumab and secukinumab achieve modest HS symptom improvement and often do not achieve complete treatment response, and many patients continue to experience draining, painful, scarring lesions, or intolerable side effects. The clinician group also noted that these treatments often fail to improve permanent lesion scarring. Consistent with expert input, the key HS treatment goals outlined by the clinician group involved reducing disease progression and the number of inflammatory lesions and improving symptoms and quality of life. The clinician group indicated that additional treatment goals include a reduction in the need for surgical intervention, prevention of comorbidities, and enabling patients to return to the workforce. According to the clinician group, an “ideal” HS treatment would result in 90% to 100% of patients achieving HiSCR50, with a large proportion achieving 90% to 100% reductions.

Consistent with input provided by the experts consulted for this review, the clinician group anticipated that bimekizumab will be used first line, adding that it could be used as monotherapy or in combination with other therapies for maintenance and/or flares. The clinician group anticipated that bimekizumab would cause a shift in the current treatment paradigm, noting that they have found it to be more efficacious than current treatments in clinical practice. The clinician group also noted that bimekizumab is the first to assess and meet higher-efficacy end points, such as HiSCR90 and HiSCR100. Both the clinical experts and clinician group emphasized the importance of aligning bimekizumab initiation criteria with those of other biologic treatments and not requiring patients to first try other biologic options. The patients identified by the clinician group as best and least suited for bimekizumab therapy aligned exactly with expert input. The clinician group did not advise the use of bimekizumab for individuals younger than 18 years or who are pregnant or breastfeeding, or in combination with other biologics, due to a lack of research in these scenarios.

A comparison-based approach to evaluating treatment response was suggested by both clinical experts and the clinician group, with baseline assessments followed by a reassessment after 4 to 6 months of treatment. Like the clinical experts, the clinician group indicated that baseline assessments should record the number and locations of inflammatory lesions (including abscesses and/or nodules), presence of tunnels and drainage, and patient-reported outcomes that focus on pain and quality of life (e.g., DLQI, HiSQoL). The criteria suggested by the clinician group for clinically significant improvement upon reassessment aligned with the experts' criteria, that is, a minimum 50% improvement in inflammatory lesion count with no disease progression, indicated by new abscesses or tunnels. For patients with HS that is responding to therapy, the clinician group noted that subsequent reassessments should be performed every 12 months, or as needed in the event of AEs or loss of response. Treatment discontinuation should be considered if no response is observed after 4 to 6 months of treatment, or if intolerable AEs or pregnancy occur. The clinician group and clinical experts agreed that bimekizumab should be initiated by practitioners with an advanced understanding of the disease and biologic therapies, such as dermatologists. However, the clinician group considered that

prescription renewal could be performed by any practitioner able to effectively assess disease severity and monitor treatment efficacy and AEs.

Drug Program Input

The drug programs provide input on each drug being reviewed through the Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized in [Table 4](#).

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert responses
Considerations for initiation of therapy	
The pivotal trials were conducted with patients aged 18 years or older. Should treatment be limited to adult patients?	The clinical experts consulted indicated that they would prescribe bimekizumab to patients aged 12 years and older. The clinical experts noted that HS usually appears around puberty, and therefore it would be appropriate to provide these treatment options to adolescents aged 12 years and older who could benefit from early treatment to prevent irreversible damage to affected areas and to manage and prevent the need for multiple surgeries in the future.
Generalizability	
The pivotal trials excluded patients with draining tunnel counts > 20 at baseline. Should such patients be eligible for treatment?	The clinical experts highlighted that they would consider prescribing bimekizumab to patients with draining tunnel counts > 20 at baseline because these patients have more severe disease and would likely benefit the most from treatment with bimekizumab.

Clinical Evidence

The objective of this clinical review report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of bimekizumab (320 mg, subcutaneous injection) for adult patients with moderate to severe HS. The focus is on comparing bimekizumab to relevant comparators and identifying gaps in the current evidence.

A summary of the clinical evidence provided by the sponsor for this review of bimekizumab is presented in 2 sections, with the critical appraisal of the evidence included at the end of each section. The first section, the systematic review, includes pivotal studies and RCTs that were selected according to the sponsor's systematic review protocol. The assessment of the certainty of the evidence in this first section using the GRADE approach follows the critical appraisal of the evidence. The second section includes indirect evidence from the sponsor.

Included Studies

Clinical evidence from the following were included in the review and appraised in this document:

- 2 RCTs identified in the systematic review
- 1 report on indirect treatment comparisons (NMA and MAIC).

Systematic Review

Contents within this section have been informed by materials submitted by the sponsor. The following has been summarized and validated by the review team.

Description of Studies

Study characteristics of the BE HEARD I and BE HEARD II trials included in the systematic review are summarized in [Table 5](#).

Table 5: Details of Studies Included in the Systematic Review

Characteristic	BE HEARD I	BE HEARD II
Designs and Populations		
Study design	Phase III, randomized, double-blind, placebo-controlled, multicentre study	Phase III, randomized, double-blind, placebo-controlled, multicentre study
Locations	86 sites were activated and enrolled patients. Regions: • Asia and Australia • Central and Eastern Europe • North America (including Canada) • Western Europe	90 sites were activated and enrolled patients. Regions: • Asia and Australia • Central and Eastern Europe • Western Europe • North America (including Canada)
Key dates	First patient enrolled: February 19, 2020 Last patient completed: February 19, 2023	First patient enrolled: March 2, 2020 Last patient completed: September 28, 2022
Randomized (N)	Total number of patients randomized: • N = 505 Initial treatment period: • Bimekizumab 320 mg q.2.w. group, n = 289 • Bimekizumab 320 mg q.4.w. group, n = 144 • Placebo group, n = 72 Maintenance treatment period: • Bimekizumab 320 mg q.2.w. followed by q.4.w. group, n = 129 • Placebo/bimekizumab 320 mg q.2.w. group, n = 65	Total number of patients randomized: • N = 509 Initial treatment period: • Bimekizumab 320 mg q.2.w. group, n = 291 • Bimekizumab 320 mg q.4.w. group, n = 144 • Placebo group, n = 74 Maintenance treatment period: • Bimekizumab 320 mg q.2.w. followed by q.4.w. group, n = 130 • Placebo/bimekizumab 320 mg q.2.w. group, n = 69
Key inclusion criteria	• ≥ 18 years old • Verifiable diagnosis of HS for at least 6 months before baseline visit • HS lesions in ≥ 2 in distinct anatomic areas, with at least 1 classified as Hurley stage II or III, at both screening and baseline • Moderate to severe HS (≥ 5 inflammatory lesions) at both screening and baseline	

Characteristic	BE HEARD I	BE HEARD II
	History of inadequate response, intolerance, or contraindication to a course of systemic antibiotics for the treatment of HS	
Key exclusion criteria	- Received prescription topical therapies for the treatment of HS within 14 days before the baseline visit - Prior treatment with an IL-17 biologic response modifier in the absence of an appropriate washout period of a minimum of 6 months or 5 half-lives - Draining tunnel count > 20 at baseline - Diagnoses of sarcoidosis, systemic lupus erythematosus, or active IBD - Has a primary immunosuppressive condition - Active infections or history of infections requiring systemic anti-infectives within the 2 months before the baseline visit - Active TB, latent TB infection, or at a high risk of exposure to TB infection - Acute or chronic HBV, HCV, or HIV - History of a lymphoproliferative disorder - Have concurrent or previous malignancy within the past 5 years before screening - Had myocardial infarction or stroke within 6 months before screening - Pregnant, breastfeeding, or planning to be pregnant within 20 weeks following the final drug dose	
Drugs		
Intervention	Bimekizumab at a dose of 320 mg administered via subcutaneous injections q.2.w. or q.4.w., depending on the treatment group.	
Comparator(s)	Matched placebo administered via subcutaneous injections q.2.w. for the first 8 injections. Patients receiving bimekizumab 320 mg q.4.w. received alternating injections of bimekizumab (q.4.w.) and placebo (q.4.w.) to maintain patient and physician blinding.	
Study duration		
Screening phase	Minimum of 14 days and up to a maximum of 5 weeks before randomization.	
Treatment phase	- Initial treatment period: 16 weeks - Maintenance treatment period: 32 weeks	
Follow-up phase	For patients not continuing in the extension study, a safety follow-up visit was completed 20 weeks after their last treatment dose.	
Outcomes		
Primary end point	HiSCR50 at week 16	HiSCR50 at week 16
Secondary and exploratory end points ^a	Secondary: - HiSCR75 at week 16 - Absolute change from baseline in DLQI total score at week 16 - Absolute change from baseline in HSSDD skin pain score at week 16 - HSSDD worst skin pain score response based on clinically meaningful change at week 16 Exploratory: - HiSCR50 rates up to week 48 - HiSCR75 rates up to week 48 - Flare by week 16 and up to week 48	Secondary: - HiSCR75 at week 16 - Flare by week 16 - Absolute change from baseline in DLQI total score at week 16 - Absolute change from baseline in HSSDD skin pain score at week 16 - HSSDD worst skin pain score response based on clinically meaningful change at week 16 Exploratory: - HiSCR50 rates up to week 48 - HiSCR75 rates up to week 48

Characteristic	BE HEARD I	BE HEARD II
	• Change from baseline in DLQI total score up to week 48 • Change from baseline in HSSDD skin pain up to week 48 • HSSQ skin pain response up to week 48 • Initiation of systemic antibiotic rescue therapy • Change from baseline in HiSQOL total score up to week 48 • Change from baseline in EQ-5D-3L VAS scores up to week 48	• Change from baseline in DLQI total score up to week 48 • Change from baseline in HSSDD skin pain up to week 48 • HSSQ skin pain response up to week 48 • Initiation of systemic antibiotic rescue therapy • Change from baseline in HiSQOL total score up to week 48 • Change from baseline in EQ-5D-3L VAS scores up to week 48
Publication status		
Publications	Publications: Kimball et al. (2024) (BE HEARD I and II) ³⁷ ClinicalTrials.gov ID: NCT04242446	Publications: Kimball et al. (2024) (BE HEARD I and II) ³⁷ ClinicalTrials.gov ID: NCT04242498

DLQI = Dermatology Life Quality Index; HBV = hepatitis B virus; HCV = hepatitis C virus; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HiSQOL = Hidradenitis Suppurativa Quality of Life; HS = hidradenitis suppurativa; HSSDD = Hidradenitis Suppurativa Symptom Daily Diary; HSSQ = Hidradenitis Suppurativa Symptom Questionnaire; IBD = inflammatory bowel disease; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; TB = tuberculosis; VAS = visual analogue scale.

^aThe secondary and exploratory outcomes listed aligned with the outcomes included in the sponsor's summary and do not include all outcomes in the trials.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

The BE HEARD I and BE HEARD II trials were phase III, randomized, double-blind, placebo-controlled, multicentre studies designed to evaluate the efficacy and safety of bimekizumab in adults (aged 18 years and older) with moderate to severe HS for at least 6 months before the baseline visit. All patients had a history of inadequate response to systemic antibiotics used for treating HS. The primary objective was the same in both trials: to evaluate the efficacy of bimekizumab in patients with moderate to severe HS, based on an HiSCR50 at week 16. The secondary objectives were also identical: to evaluate the efficacy of bimekizumab on other measures of disease activity, and the safety of bimekizumab, in patients with moderate to severe HS. Secondary efficacy end points were also assessed at week 16, and the measures of disease activity included the HiSCR75, absolute change from baseline in DLQI total score, absolute change in skin pain score as per the HSSDD, and skin pain response based on a clinically meaningful change from baseline in the HSSDD. These outcomes are described in detail in the Outcomes section of this report. Of note, the BE HEARD II trial included 1 additional measure of disease activity as a secondary efficacy end point, the occurrence of a flare by week 16.

Both studies consisted of 3 core study periods ([Figure 1](#)): an initial screening period (from week –5 to week 0), double-blind initial treatment period (16 weeks), and a double-blind 48-week treatment period. In addition, patients who did not continue in the extension study, including those who withdrew from treatment and those who completed all study visits, had a safety follow-up visit 20 weeks after their final dose of treatment. The initial screening period was designed for washout of nonpermitted medications, laboratory data collection, and verification that doses of concomitant and permitted medications were stable. The 48-week treatment period comprised a placebo-controlled 16-week initial treatment period, followed by a 32-week maintenance treatment period during which all patients received bimekizumab. The initial treatment period was used to

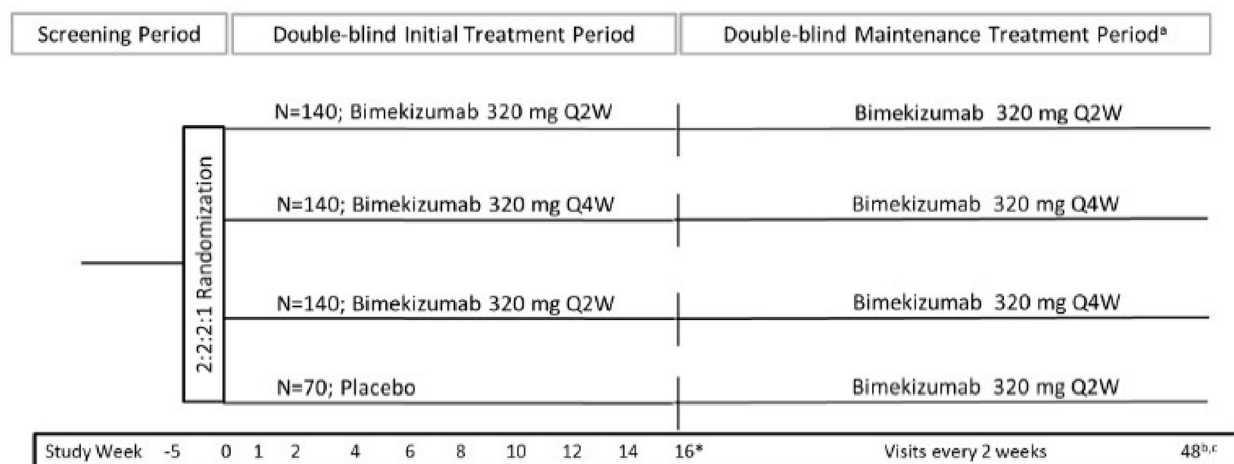
demonstrate the efficacy of bimekizumab compared to placebo, while the 32-week maintenance treatment period was used to collect information on safety and efficacy beyond initial treatment. Patients who completed week 48 of the maintenance treatment period were eligible to continue receiving bimekizumab in the ongoing long-term extension study if an improvement of at least 25% in AN count was achieved.

Randomization (2:2:2:1) was stratified by Hurley stage (II or III) and current antibiotic use (yes or no) into the following treatment groups:

- bimekizumab 320 mg every 2 weeks for the initial treatment period (week 0 to 16) and the maintenance treatment period (week 16 to 48)
- bimekizumab 320 mg every 4 weeks for the initial treatment period (week 0 to 16) and the maintenance treatment period (week 16 to 48)
- bimekizumab 320 mg every 2 weeks for the initial treatment period (week 0 to 16) to every 4 weeks for the maintenance treatment period (week 16 to 48)
- placebo for the initial treatment period (week 0 to 16) to bimekizumab 320 mg every 2 weeks for the maintenance treatment period (week 16 to 48).

The 2 trials enrolled 505 patients (BE HEARD I) and 509 patients (BE HEARD II) across 176 centres in Asia and Australia (Australia, Israel, Japan), Central and Eastern Europe (Bulgaria, Czechia, Hungary, Poland), Western Europe (France, Germany, Ireland, Italy, Spain, UK), and North America (Canada, US). There were 30 patients (5.9%) in the BE HEARD I trial and 36 (7.1%) in the BE HEARD II trial in centres across Canada.

The recommended dosing approved by Health Canada is bimekizumab 320 mg every 2 weeks for the first 16 weeks followed by bimekizumab 320 mg every 4 weeks thereafter. Within each study, data were pooled from the 2 groups that received bimekizumab 320 mg every 2 weeks during the initial treatment period and formally compared to data from the placebo group at week 16. In addition, data from the 2 groups that switched regimens for the maintenance treatment period are presented as supporting evidence from week 16 to 48, which includes the group that switched from placebo in the initial treatment period to bimekizumab every 2 weeks for the maintenance treatment period and the group that switched from bimekizumab every 2 weeks in the initial treatment period to every 4 weeks for the maintenance treatment period. Data cut-offs were February 19, 2023, in the BE HEARD I trial, and September 28, 2022, in the BE HEARD II trial.

Figure 1: Study Schematic for BE HEARD I and BE HEARD II Studies

HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; Q2W = every 2 weeks; Q4W = every 4 weeks.

*Week 16 = primary efficacy end point (HiSCR50 in the bimekizumab group versus in the placebo group).

^aStudy participants in both trials were permitted to withdraw from the study from week 32 onwards if no partial response was achieved (partial response was defined as $\geq 25\%$ improvement in abscess and inflammatory nodule count relative to baseline [week 0] lesion values).

^bStudy participants with $\geq 25\%$ improvement in abscess and inflammatory nodule count were permitted to continue into the extension study (HS0005).

^cTwenty-week safety follow-up (from last drug injection) for any study participant who discontinued study treatment before week 48, or who did not continue into the HS0005 study.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Populations

Inclusion and Exclusion Criteria

Patients enrolled in the BE HEARD I and II trials were 18 years and older, with a verifiable diagnosis of HS, based on a clinical history and physical examination, for at least 6 months before the baseline visit. At both screening and baseline visits, patients were required to have a minimum of 2 HS lesions in 2 anatomically distinct areas, with at least 1 lesion classified as Hurley stage II or III. Moderate to severe HS was defined as the presence of at least 5 inflammatory lesions (i.e., number of abscesses plus number of inflammatory nodules). The patients enrolled in both trials had a history of an inadequate response to systemic antibiotics used for treating HS. Inadequate response was defined as a demonstrated intolerance to systemic antibiotics (before or developed during initial therapy); a contraindication to systemic antibiotics; or an original response to course(s) of systemic antibiotics, followed by a recurrence of HS after antibiotic discontinuation.

In both the BE HEARD I and II trials, patients who had received an IL-17 biologic response modifier were excluded unless they undertook a minimum washout period of 6 months or 5 half-lives before the baseline visit, whichever was longer. Patients were also excluded from both studies if they had received a prescription topical therapy for HS and did not undergo a minimum 14-day washout period before the baseline visit, or if they exhibited any medical or psychiatric conditions that could impact their ability to participate, as determined by the investigator. Patients were excluded from both studies if they had a draining tunnel count greater than 20, the presence of any other active skin condition that could interfere with HS assessment, in the opinion of the investigator, a diagnosis of sarcoidosis, systemic lupus erythematosus, active IBD, and/or a primary immunosuppressive condition, or if they were receiving immunosuppressant therapies

following organ transplant. Other reasons for excluding patients included active infection or a recent history of systemic treatment or hospitalization due to infection, active tuberculosis latent TB infection, or at a high risk of exposure to TB infection, acute or chronic hepatitis B virus, hepatitis C virus, or HIV. Breastfeeding patients, currently pregnant patients, or patients planning to be pregnant within 20 weeks of their last drug dose were also excluded from the trials.

Interventions

Bimekizumab was administered as a 320 mg dose every 2 weeks or every 4 weeks via 2 prefilled 1 mL syringes (160 mg/mL) according to the treatment group dosing schedule. Bimekizumab is currently approved by Health Canada as a 320 mg/2 mL dosage administration (given as 2 subcutaneous injections of 160 mg/1 mL or 1 subcutaneous injection of 320 mg/2 mL). The 320 mg/2 mL dosage bolus administration regimen was not investigated in the BE HEARD I and II trials. Placebo treatment consisted of saline administered as 2 subcutaneous 1 mL injections. To maintain blinding, patients in the placebo group received saline every 2 weeks and patients who received bimekizumab 320 mg every 4 weeks received alternating injections (every 2 weeks) of bimekizumab and placebo. All injections were administered by unblinded study personnel at the investigation sites.

In the BE HEARD I and II trials, certain concomitant medications, procedures, and therapies were permitted. These included wound care (limited to alginates, hydrocolloids, and hydrogels), lesion care (saline, water, and/or petroleum jelly), non-opioid analgesic therapy (if a patient's pain worsened after baseline or if a patient was receiving a stable [scheduled] dose of a non-opioid analgesic for HS-related pain or for a non-HS medical condition), and antibiotic therapy for patients who entered the study on a stable dose regimen of systemic tetracycline, doxycycline, or minocycline antibiotics. Antibiotics taken on a short-term or intermittent (i.e., as needed) basis were not considered a stable dose. Patients were permitted antibiotic therapy past week 16 if required, based on investigator judgment. If pain worsened after baseline, ibuprofen was permitted for HS-related pain (at a dose of up to 800 mg orally every 6 hours, not to exceed 3.2 g every 24 hours) and/or acetaminophen as per the product monograph. For non-HS-related pain, initiation of any new analgesic or other treatment excluded opioids. In both studies, prohibited concomitant medications and therapies included immunomodulatory therapies such as topical or systemic steroids, (psoralen and UVA, and/or UVB), or photochemotherapy, surgical and laser interventions for HS, topical and systemic HS therapies, and all biologic therapies with a potential impact on HS disease.

Any systemic antibiotic that was initiated (a new antibiotic or change in the dose or type of current antibiotic) on or after baseline (first day of drug administration) was considered rescue medication in both the initial and maintenance treatment periods. There were no absolute restrictions on the use of rescue medications for patients who experienced deterioration in HS. Antibiotics initiated during the initial treatment period based on disease flare or other extenuating circumstances were discussed with the medical monitor. Patients who received any systemic antibiotics or systemic antibiotics for HS, as identified by the investigator, were recorded as nonresponders at the time of rescue medication administration and all subsequent time points. In the event of an acutely painful lesion that required immediate intervention, pain was managed as deemed appropriate by the investigator and pain medication was permitted. Possible interventions included short-

term use of analgesics, intralesional injections of triamcinolone (up to 20 mg across all lesions at a given visit, and maximum concentration of 20 mg/mL in an aqueous solution for injection), and/or incision and drainage of the abscess. Concomitant use of wound care dressings was permitted but limited to alginates, hydrocolloids, and hydrogels.

During the initial treatment period (from baseline visit to week 16), a total of 2 protocol-allowed interventions were permitted. Analgesic rescue treatment was not included in the number of protocol-allowed interventions. An intervention could have occurred on a maximum of 2 different lesions at the same visit, or on the same lesion at 2 different study visits. However, the same lesion could not be treated twice at the same visit. If a patient required more than 2 interventions within the first 16 weeks of the study, study discontinuation was recommended. The approach to rescue medications in the maintenance treatment period (week 16 to 48) was consistent with the approach in the initial treatment period, except that within each 4-week period, it was not permitted to administer the same type of intervention twice for the same lesion. In addition, if a study participant required more than 2 interventions within a 4-week period or had 2 of the same interventions on the same lesion within that period, study discontinuation was recommended.

Outcomes

A list of efficacy end points assessed in this review is provided in [Table 6](#), and descriptions of the outcome measures and their measurement properties in [Table 7](#). Summarized end points are based on outcomes included in the sponsor's Summary of Clinical Evidence as well as any outcomes identified as important to this review by the consulted clinical experts, patient and clinician groups, and public drug plans. The list of end points was finalized in consultation with expert committee members, based on end points that would be most relevant to informing committee deliberations. GRADE was used to summarize efficacy end points and notable harms outcomes.

Table 6: Summary of Outcomes From the Studies Included in the Systematic Review

Outcome measure	Time point	BE HEARD I	BE HEARD II
HiSCR50	Week 16	Primary ^a	Primary ^a
HiSCR75	Week 16	Secondary ^a	Secondary ^a
Flare	Week 48	Other	Other
Change from baseline in DLQI total score	Week 16	Secondary ^a	Secondary ^a
HSSDD worst skin pain responder rate based on clinically meaningful within-patient change	Week 16	Secondary ^a	Secondary ^a
Change from baseline in HiSQOL total score	Up to week 48	Other	Other
Safety	Up to week 48	Other	Other

DLQI = Dermatology Life Quality Index; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HiSQOL = Hidradenitis Suppurativa Quality of Life; HSSDD = Hidradenitis Suppurativa Symptom Daily Diary.

^aStatistical testing for these end points was adjusted for multiple comparisons; slightly different hierarchies were used in the BE HEARD I and II trials.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Hidradenitis Suppurativa Clinical Response 50

The primary outcome in the BE HEARD I and II trials was the proportion of patients who achieved HiSCR50 at week 16, which was defined as a greater than or equal to 50% reduction from baseline in the total AN count, with no increase from baseline in the number of abscesses and/or draining tunnels. Patients with HS that reached the threshold for HiSCR50 have demonstrated a clinically meaningful within-patient improvement.³⁸ The HiSCR50 measure has been validated in patients with HS, showing weak to moderate correlation with other physician-related assessments, and it has demonstrated reliability and responsiveness in this population.³⁸ The sponsor did not identify an MID for the between-group difference in HiSCR50.

HiSCR75 at week 16 was a ranked secondary outcome in the BE HEARD I and II trials. HiSCR75 was defined as a greater than or equal to 75% reduction from baseline in the total AN count, with no increase from baseline in the number of abscesses and/or draining tunnels. The sponsor did not identify an MID for the between-group difference in HiSCR75.

Flare

In the BE HEARD II trial, HS flare by week 16 was included as a ranked secondary outcome and analyzed descriptively in the BE HEARD I trial. An HS disease flare was defined as a minimum 25% increase in AN count, with an absolute increase greater than or equal to 2 AN counts relative to baseline. A patient's disease flare status was reported as "yes" or "no" at each visit, and the proportion of patients who experienced a flare was calculated in each treatment group. The absence of a flare was considered a clinically meaningful outcome. The sponsor did not identify an MID for the between-group difference in flare rates.

DLQI Total Score

Change from baseline in DLQI total score was assessed at week 16 as a ranked secondary outcome in both BE HEARD I and II trials; assessments were conducted at baseline, week 4, week 8, week 12, week 16, week 20, week 32, week 36, and week 48. The DLQI is a skin disease questionnaire designed to evaluate how symptoms and treatments affect an individual's HRQoL; it has been previously used to assess patients with HS.³⁹⁻⁴¹ The DLQI tool includes domains regarding symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The DLQI scale ranges from 0 to 30, with higher scores indicating lower overall HRQoL. In other dermatological or skin conditions, a 4-point decrease in the DLQI total score (DLQI response) has been reported to be meaningful for the patient (i.e., a within-patient MCID), while a DLQI total absolute score of 0 or 1 indicates no or small impact of the disease on HRQoL.⁴² An anchored-based approach by Basra et al. (2012)³⁹ was used to determine MCID thresholds for the DLQI in a patient population living with 20 different acute or chronic skin conditions. Thus, in the BE HEARD I and II trials, a within-group and between-group decrease greater than or equal to 4 points in the DLQI total score was considered clinically meaningful.

Hidradenitis Suppurativa Symptom Daily Diary

In the BE HEARD I and II trials, a secondary end point was the HSSDD worst skin pain score response based on a clinically meaningful change for the worst skin pain item among patients with a score of 3 or more at baseline. The HSSDD responses were collected daily from screening through to the week 16 visit. The HSSDD was developed to capture patients' experience with key symptoms associated with moderate

to severe HS. The full instrument captures 5 domains: skin pain at its worst, skin pain on average, itch at its worst, smell or odour, and drainage or oozing from HS lesions. These items are ranked on an 11-point numerical rating scale ranging from 0 to 11, with higher scores indicate more severe symptoms. For the worst skin pain domain, a score of 0 represents “no skin pain” and 11 represents a “skin pain as bad as you can imagine.” An anchor-based approach (using Patient Global Impression of Severity and Patient Global Impression of Change scales) with pooled, blinded data from BE HEARD trial participants with moderate to severe HS was used to calculate a clinically meaningful within-patient change of 3- to 4-point decrease (i.e., 30% to 40% of the scale range) in worst skin pain score. A clinically meaningful change for the worst skin pain item was defined as at least a 3-point reduction from baseline in HSSDD among BE HEARD trial participants with a score of 3 or more at baseline, based on weekly averages. The sponsor did not identify a published MID for the between-group difference for HSSDD worst skin pain responder rate.

Hidradenitis Suppurativa Quality of Life

In the BE HEARD I and II trials, the HiSQOL tool was utilized as an HS-specific measure of HRQoL at baseline, week 4, week 16, week 32, and week 48. This tool includes 17 items assessed over a 7-day recall period on a Likert-type verbal rating level scale with 5 to 7 response levels. These items are grouped into 3 subscales assessing symptoms (4 items), psychosocial impact (5 items), and activities and adaptations (8 items). For all items, the score ranges from 0 (not at all) to 4 (extremely). Three subscale scores and a total score (0 to 68 points) are derived by summing the item scores. Across all scores, a higher number indicates a more severe impact on HRQoL. Definitions of within-patient MCID thresholds for the HiSQOL domains, based on thresholds estimated using the anchor-based approach (using Patient Global Impression of Severity and Patient Global Impression of Change scales) with pooled, blinded data from trial participants with moderate to severe HS, are as follows: symptoms subscale (5- to 6-point decrease); psychosocial impact subscale (4- to 5-point decrease); activities-adaptation subscale (10- to 11-point decrease); and total score (20- to 21-point decrease).⁴³ The sponsor did not identify a published MID value for the between-group difference in the HiSQOL total score.

Safety Analyses

Safety analyses conducted for both BE HEARD I and II trials included extent of exposure to bimekizumab or placebo, all treatment-emergent adverse events, serious TEAEs, TEAEs leading to study withdrawal, and deaths due to TEAEs. Additional safety end points focused on AEs of special interest, which included potential Hy's Law cases, infections, suicidal ideation and behaviour, major adverse cardiovascular events, hepatic events, potential drug-induced liver injury and malignancies, and inflammatory bowel disorder. All TEAEs and SAEs were recorded from the signing of the informed consent form until the safety follow-up visit, with monitoring until resolution, stabilization, the investigator determined that the AE was no longer clinically significant, or the participant was lost to follow-up.

Table 7: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
Hidradenitis Suppurativa Clinical Response (HiSCR)	Physician-assessed measure of response to treatment based on the status of 3 types of lesions: abscesses, inflammatory nodules, and draining fistulae. HiSCR50 and HiSCR75 represent a minimum 50% or 75% reduction in AN count, respectively, with no increase from baseline in the number of abscesses and/or draining fistulae. At week 16, HiSCR50 was defined as a primary outcome and HiSCR75 as a secondary outcome in the BE HEARD I and BE HEARD II trials.	Validity: In 1 study with patients with HS, there were weak to moderate correlations between HiSCR50 and other physician-rated assessments (Hurley stage, MSS, and HS-PGA) and PRO measures (Pain-VAS, DLQI, and WPAI: SHP) (Spearman rho, -0.61 to -0.27).³⁸ Test-retest reliability: Strong correlation with AN count between screening and baseline visit (ICC = 0.91).³⁸ Responsiveness: HiSCR50 achievers showed meaningful improvements in all PROs.^{38,44}	Several studies suggest that a threshold of 50% (i.e., HiSCR50) is clinically meaningful for assessing response. ^{38,45}
Dermatology Life Quality Index (DLQI)	Self-administered HRQoL assessment tool for adults with skin diseases that includes 6 domains, with the sum corresponding to a total score. The range of scores is 0 to 30, with a higher score indicating lower HRQoL.⁴⁵ Change from baseline in DLQI total score at week 16 was defined as a secondary end point in the BE HEARD I and II trials.	Validity: In 1 study with patients with HS, DLQI was moderately to strongly correlated with EQ-5D-5L, EQ VAS, DLQI-Relevant and Skindex-16 total scores (range, 0.49 to 0.99). There were weak or moderate correlations with HS-PGA (0.35 to 0.43) and MSS (0.32 to 0.39).⁴⁶ Reliability and responsiveness: No evidence identified	Among adult patients with moderate to severe HS and baseline DLQI ≥ 4 , the MID for meaningful within-patient improvement was defined as at least a 4-point decrease. ^{42,47}
Hidradenitis Suppurativa Symptom Daily Diary (HSSDD)	Daily assessment tool capturing 5 domains: worst skin pain, skin pain on average, itch at its worst, smell or odour, and drainage or oozing from HS lesions. Items are ranked on an 11-point numerical rating scale, with higher scores indicating more severe symptoms.⁴⁸ At week 16, HSSDD worst skin pain responder rate and change from baseline in score were defined as secondary end points in the BE HEARD I and II trials.	Data from the BE HEARD I and BE HEARD II trials were used to determine measurement properties of electronic versions of the HSSDD and HSSQ. Validity: Convergent or divergent validity was sufficient, with all correlations in the prespecified direction and strength. The eHSSDD demonstrated appropriate known-groups validity, as item scores discriminated between subgroups defined by Hurley stage measurements at baseline and week 15.⁴⁸ Reliability: Test-retest reliability analyses demonstrated sufficient item score reproducibility for eHSSDD between baseline and	An anchor-based approach (using PGI-S and PGI-C scales) with pooled, blinded data from BE HEARD trial participants with moderate to severe HS was used to calculate that a clinically meaningful within-patient change is a 3- to 4-point decrease (i.e., 30% to 40% of the scale range) in the worst skin pain score. ⁴⁹

Outcome measure	Type	Conclusions about measurement properties	MID
		week 4 (ICC = 0.80 to 0.85), exceeding the prespecified threshold of acceptability (ICC = 0.70).⁴⁸ Responsiveness: Week 16 changes from baseline in eHSSDD item scores and PGI scale anchors showed moderate to strong correlation.⁴⁸	

AN = abscess and inflammatory nodule; DLQI = Dermatology Life Quality Index; eHSSDD = electronic Hidradenitis Suppurativa Symptom Daily Diary; HiSCR = Hidradenitis Suppurativa Clinical Response; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HRQoL = health-related quality of life; HS = hidradenitis suppurativa; HSSDD = Hidradenitis Suppurativa Symptom Daily Diary; HSSQ = Hidradenitis Suppurativa Symptom Questionnaire; ICC = intraclass correlation coefficient; MID = minimal important difference; MSS = Modified Sartorius scale; PGA = Physician's Global Assessment; PGI = Patient Global Impression; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PRO = patient-reported outcome; SHP = Specific Health Problem; VAS = visual analogue scale; WPA = Work Productivity and Activity.

Source: Sponsor's Summary of Clinical Evidence.

Statistical Analysis

Sample Size and Power Calculations

A sample size of 490 was planned for each study and randomization was scheduled at a 2:2:2:1 ratio into 4 treatment groups in the initial treatment period:

- n = 140, bimekizumab 320 mg every 2 weeks during the initial treatment period and the maintenance treatment period
- n = 140, bimekizumab 320 mg every 2 weeks during the initial treatment period and then bimekizumab 320 mg every 4 weeks during the maintenance treatment period
- n = 140, bimekizumab 320 mg every 4 weeks during the initial treatment period and the maintenance treatment period
- n = 70, placebo every 2 weeks during the initial treatment period and then bimekizumab 320 mg every 2 weeks during the maintenance treatment period.

The analyses of the primary and secondary efficacy end points were based on a comparison of bimekizumab versus placebo at week 16, with alpha-adjustment strategy (as shown in [Figure 2](#) and [Figure 3](#)) based on a familywise error rate of 0.025 ($\alpha = 0.05/2$). A pooled group (which consisted of patients randomized into the group receiving bimekizumab 320 mg every 2 weeks during the initial treatment period and the maintenance treatment period and the group receiving bimekizumab 320 mg every 2 weeks during the initial treatment period and then bimekizumab 320 mg every 4 weeks during the maintenance treatment period) was established for the analyses of the primary and key secondary outcomes in both studies before the randomization of patients and power calculation, and assumptions were established to support the regulatory request.

Sample size calculations for both trials were driven by change from baseline in worst skin pain at end point. At a 2-sided significance level of 0.025, a sample size of 140 (bimekizumab 320 mg every 4 weeks) to

70 (placebo) provided 73% power to detect at least a 1.5 difference for bimekizumab versus placebo for change from baseline in worst skin pain. Power calculation methods and assumptions for other outcomes of interest in both studies are presented in [Table 8](#). The randomization ratio of 2:2:2:1 was chosen to increase the probability of patients being randomized to active treatment in the initial treatment period.

In both studies, 99% power was needed to detect a statistically significant difference for the primary outcome (HiSCR50) for the pooled data of bimekizumab 320 mg every 2 weeks versus placebo at alpha of 0.025 (2-sided), assuming that the proportion of patients with a response in the pooled bimekizumab 320 mg every 2 weeks group was 0.6 and in the placebo group was 0.25. Given the high power (greater than 89%) calculations and assumptions outlined for the primary and secondary end points at a 2-sided significance level (0.025) and per the alpha-spending strategy for the pooled bimekizumab 320 mg every 2 weeks versus placebo comparison, it was likely that the comparison of bimekizumab every 4 weeks versus placebo for change from baseline in worst skin pain could be tested at a 0.05 level of significance (corresponding to 81% power).

After study patients were randomized in both studies, an additional end point, worst skin pain response (based on a threshold for clinically meaningful change, defined as a ≥ 3 -point decrease from baseline in HSSDD weekly worst skin pain score at week 16 among patients with a score of ≥ 3 at baseline), was included in the sequential testing procedure (protocol amendments). At a 2-sided significance level of 0.025, a new sample size of 104 (bimekizumab every 4 weeks) to 52 (placebo) patients in the subset of study participants reporting baseline HSSDD worst skin pain score at or beyond the threshold for clinically meaningful change (baseline HSSDD ≥ 3) provided 53% power to detect a statistically significant difference between bimekizumab every 4 weeks, versus placebo in the proportion of patients with a worst skin pain response. In addition, the bimekizumab 320 mg every 4 weeks comparison of worst skin pain response versus placebo against the 0.05 level of significance was considered likely at 65% power. Given the strength of the power for the bimekizumab 320 mg every 2 weeks arm versus the placebo arm across end points, a low power for the final end point in the bimekizumab every 4 weeks versus placebo comparison was considered acceptable.

Table 8: Power Calculation Methods and Assumptions (BE HEARD I and BE HEARD II Studies)

End point	Power Alpha = 0.025, 2-sided		Assumptions		
	q.2.w.	q.4.w.	Week 16 BKZ q.2.w. N = 280 ^a	Week 16 BKZ q.4.w. N = 140	Week 16 Placebo N = 70
HiSCR50	0.99	0.90	Proportion of responders = 0.60	Proportion of responders = 0.50	Proportion of responders = 0.25
HiSCR75	0.99	0.98	Proportion of responders = 0.45	Proportion of responders = 0.35	Proportion of responders = 0.10

End point	Power Alpha = 0.025, 2-sided		Assumptions		
	q.2.w.	q.4.w.	Week 16 BKZ q.2.w. N = 280 ^a	Week 16 BKZ q.4.w. N = 140	Week 16 Placebo N = 70
Flare	0.99	0.99	Proportion of participants with flare by week 16 = 0.09	Proportion of participants with flare by week 16 = 0.19	Proportion of participants with flare by week 16 = 0.52
DLQI	0.99	0.96	Mean CFB = -5.4 SD = 6.8	Mean CFB = -4.8 SD = 6.8	Mean CFB = -0.8 SD = 6.6
Worst skin pain CFB ^b	0.89	0.73	Mean CFB = -2.2 SD = 3.2	Mean CFB = -2.0 SD = 3.2	Mean CFB = -0.5 SD = 3.7
Worst skin pain response ^c	0.95	0.53	Proportion of responders = 0.53	Proportion of responders = 0.43	Proportion of responders = 0.23

BKZ = bimekizumab; CFB = change from baseline; DLQI = Dermatology Life Quality Index; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation.

Note: Estimates for the BE HEARD II study were based on week-12 data from a phase II study of bimekizumab (HS0001).

^aPooled from the group receiving BKZ 320 mg q.2.w. in both the initial and the maintenance treatment periods and the group receiving BKZ 320 mg q.2.w. arm in the initial treatment period and BKZ 320 mg q.4.w. in the maintenance treatment period.

^bWithin-patient average of worst skin pain score, according to 24-hour recall.

^cAssumes N = 208, 104, and 52 in the q.2.w., q.4.w., and placebo groups, respectively, to account for worst skin pain score at ≥ 3 (i.e., the threshold for clinically meaningful change from baseline).

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Statistical Testing

[Table 9](#) provides a summary of the statistical models, missing data imputation methods, and sensitivity analyses for the primary and secondary end points in the BE HEARD I and II trials.

A logistic regression model with fixed effects was used to evaluate the primary (HiSCR50) and binary secondary end points. For HiSCR50, the fixed effects were treatment, Hurley stage at baseline, and baseline antibiotic use. The fixed effects were the same for HiSCR75 at week 16 in the BE HEARD I and II trials and flare by week 16 in the BE HEARD II trial. For the secondary end point HSSDD skin pain responder rate by week 16, the logistic regression model used the same fixed effects plus analgesic use.

Primary and Key Secondary End Points

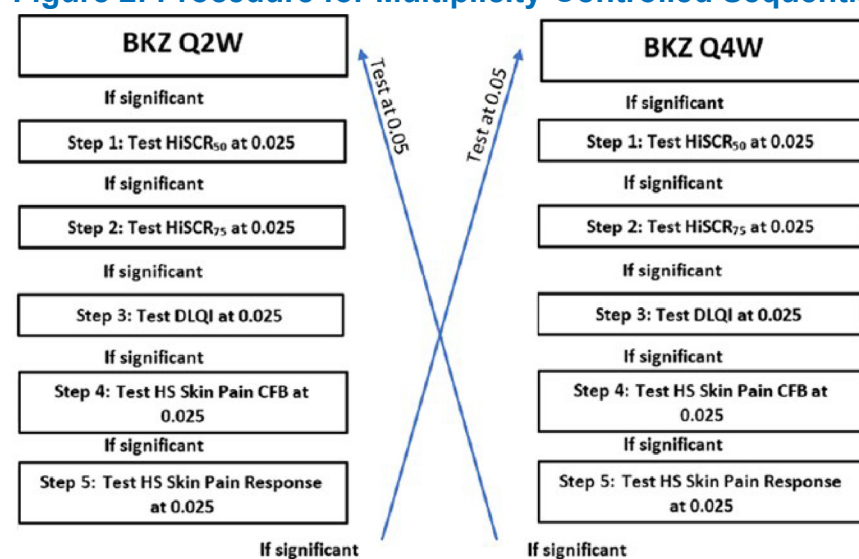
The primary and key secondary end points of the BE HEARD I trial were ranked ([Figure 2](#)), and statistical testing was performed using parallel gatekeeping frameworks to control for the overall type I error rate at 0.05. In these frameworks, each bimekizumab dose (320 mg every 2 weeks and 320 mg every 4 weeks) was compared with placebo in the first instance at a familywise error rate of 0.025 (alpha = 0.05/2). Within each dose, simultaneously, closed testing for the primary and subsequent secondary efficacy end points was performed. In the BE HEARD I trial, step 1 tests the primary efficacy end point (HiSCR50 at week 16) up to step 5 (clinically meaningful HSSDD skin pain response). Therefore, the primary end point was evaluated at a 0.025 significance level followed by a sequential testing of the ranked secondary end points. Testing only continued if a significance of 0.025 was achieved in the previous end point. If step 5 was significant at the

0.025 level within the dose currently being evaluated (i.e., bimekizumab every 2 weeks), then testing of steps 1 to 5 in the other dose (i.e., bimekizumab every 4 weeks) would be repeated at a significance level of 0.05.

In the BE HEARD II trial, a similar multiplicity-controlled parallel gatekeeping framework at the same significance level as in the BE HEARD I trial were used. One notable difference between the frameworks of the 2 trials was the inclusion of flare by week 16 as a key secondary end point in the BE HEARD II trial. Thus, the primary sequential testing of end points at 0.025 occurred for steps 1 to 6; if step 6 was significant, testing of steps 1 to 6 in the other dose was repeated at the 0.05 significance level ([Figure 3](#)). The analyses of step 5 in the BE HEARD I trial and step 6 in the BE HEARD II trial did not reach significance at the 0.025 level. Therefore, all end points were only tested at a significance level of 0.025 for both studies.

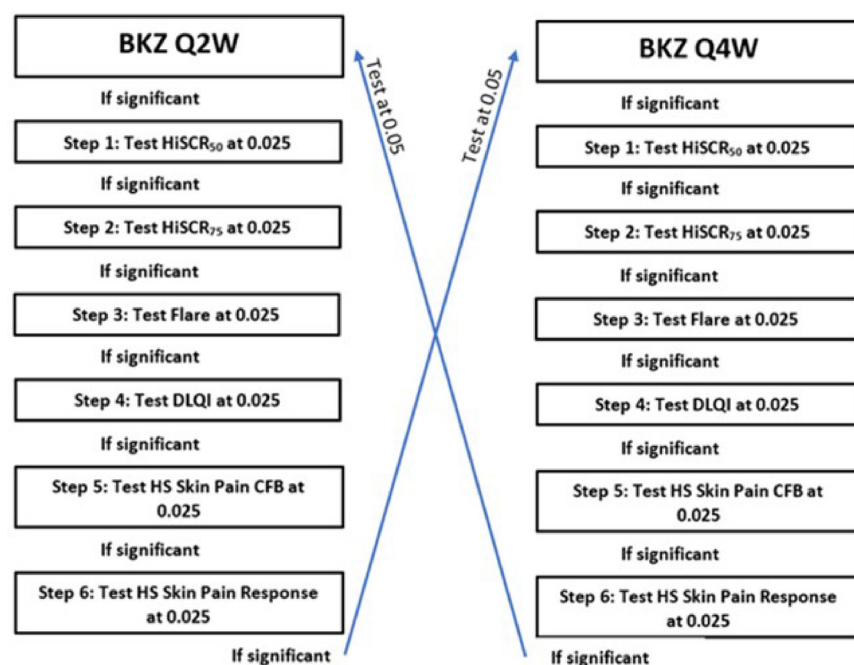
For continuous end points, an analysis of covariance with fixed effects of treatment, Hurley stage at baseline, baseline antibiotic use, and analgesic use (only for skin pain analyses) with a covariate of baseline value was used. This statistical testing strategy was employed for the following secondary end points in both the BE HEARD I and II trials: change from baseline in DLQI total score by week 16 and change from baseline in HSSDD worst skin pain score.

Figure 2: Procedure for Multiplicity-Controlled Sequential Testing in BE HEARD I Study



BKZ = bimekizumab; CFB = change from baseline; DLQI = Dermatology Life Quality Index; HiSCR₅₀ = Hidradenitis Suppurativa Clinical Response 50; HiSCR₇₅ = Hidradenitis Suppurativa Clinical Response 75; HS = hidradenitis suppurativa; Q2W = every 2 weeks; Q4W = every 4 weeks.

Source: BE HEARD I Clinical Study Report.¹⁶ Details included in the figure are from the sponsor's Summary of Clinical Evidence.

Figure 3: Procedure for Multiplicity-Controlled Sequential Testing in BE HEARD II Study

BKZ = bimekizumab; CFB = change from baseline; DLQI = Dermatology Life Quality Index; HiSCR₅₀ = Hidradenitis Suppurativa Clinical Response 50; HiSCR₇₅ = Hidradenitis Suppurativa Clinical Response 75; HS = hidradenitis suppurativa; Q2W = every 2 weeks; Q4W = every 4 weeks.

Source: BE HEARD II Clinical Study Report.¹⁷ Details included in the figure are from the sponsor's Summary of Clinical Evidence.

Data Imputation Methods

Data imputation techniques employed in the 2 trials were similar for the primary and secondary outcomes assessed in the BE HEARD I and BE HEARD II trials. For the primary end point, if a study participant experienced an intercurrent event, the primary efficacy variables at that time point and all subsequent time points (whether the data were observed or not) were treated as “nonresponses,” that is, as though the study participant had not met the criteria for response based on the composite estimand. All remaining missing data for the primary end point were imputed using multiple imputation (MI) Markov Chain Monte Carlo (MCMC) monotone regression method for the primary analysis.

For the secondary binary efficacy end points, intercurrent events were handled and missing data were imputed using the same methods as for the primary efficacy end point. For secondary continuous efficacy end points, MI-MCMC monotone regression was the primary imputation method, with last observation carried forward used if the model could not converge.

For the continuous secondary end points in the BE HEARD I and II trials (i.e., change from baseline in DLQI total score and HSSDD skin pain scores at week 16), a hypothetical estimand strategy was applied in the primary analysis. In this approach, missing data or intercurrent events (such as any antibiotic use) were imputed using an MI model (i.e., the result for that visit was treated as missing and the data were imputed). For continuous outcomes, the primary analysis in the BE HEARD I and II trials was analyzed using MI with any antibiotic use. Sensitivity analysis using MI with HS-specific antibiotic use as an intercurrent event was

also conducted. To ensure the analysis of primary and secondary end points were consistent across the various datasets in the BE HEARD I and II trials, efficacy analyses were repeated for different datasets (Table 9).

Table 9 provides a summary of the statistical models and missing data imputation methods for the BE HEARD I and II trials, where *mNRI (ALL-ABX)* refers to a modified nonresponder imputation method in which any antibiotic use was treated as an intercurrent event and *MI (ALL-ABX)* refers to an MI-MCMC monotone regression method in which any antibiotic use was treated as an intercurrent event.

Sensitivity Analyses

A series of sensitivity analyses for the primary efficacy end points were performed to evaluate the assumptions related to the handling of missing data using nonresponse imputation, MI-MCMC reference-based imputation, and tipping-point analysis. Sensitivity analyses were performed on the full analysis set, the per-protocol set, and the COVID-19-free set populations. For secondary binary efficacy end points, nonresponder imputation and observed case methods were used for sensitivity analyses.

Table 9: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
BE HEARD I and BE HEARD II				
HiSCR50 at week 16 (binary/responder)	Logistic regression model with fixed effects	Fixed effects: Treatment, Hurley stage at baseline (II or III), baseline antibiotic use (yes or no)	mNRI (ALL-ABX) ^a	Performed based on the FAS, PPS, and CFS. mNRI (HS-ABX) ^b and OC
HiSCR75 at week 16 (binary/responder)	Logistic regression model with fixed effects	Fixed effects: Treatment, Hurley stage at baseline (II or III), baseline antibiotic use (yes or no)	mNRI (ALL-ABX) ^a	Performed based on the CFS. mNRI (HS-ABX) ^b and OC
Flare by week 16 (binary/responder)	Logistic regression model with fixed effects	Fixed effects: Treatment, Hurley stage at baseline (II or III), baseline antibiotic use (yes or no)	mNRI (ALL-ABX) ^a	The following sensitivity analyses were only performed in the BE HEARD II trial due to flare by week 16 being ranked as a secondary end point: - Performed based on the CFS. - mNRI (HS-ABX)^b and OC
Change from baseline in DLQI total score at week 16 (continuous)	ANCOVA with fixed effects	Fixed effects: Treatment, Hurley stage at baseline (II or III), baseline antibiotic use (yes or no) Covariate: Baseline DLQI value	MI (ALL-ABX) ^c	Performed based on the CFS. MI (HS-ABX) ^d

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
HSSDD skin pain responder rate based on clinically meaningful within-patient change at week 16 (binary/responder)	Logistic regression model with fixed effects	Fixed effects: Treatment, Hurley stage at baseline (II or III), baseline antibiotic use (yes or no), and analgesic use	mNRI (ALL-ABX) ^a	Performed based on the CFS. mNRI (HS-ABX) ^b and OC

ALL-ABX = any antibiotic use; ANCOVA = analysis of covariance; CFS = COVID-19-free set; DLQI = Dermatology Life Quality Index; FAS = full analysis set; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HS = hidradenitis suppurativa; HS-ABX = hidradenitis suppurativa-specific antibiotic use; HSSDD = Hidradenitis Suppurativa Symptom Daily Diary; MCMC = Markov Chain Monte Carlo; MI = multiple imputation; mNRI = modified nonresponder imputation; OC = observed case; PPS = per-protocol set.

^aRefers to an mNRI method in which any antibiotic use (ALL-ABX) was treated as an intercurrent event (conservative definition).

^bRefers to an mNRI method in which only HS-specific antibiotic use (HS-ABX) was treated as an intercurrent event (restrictive definition).

^cRefers to an MI-MCMC monotone regression method in which any antibiotic use (ALL-ABX) was treated as an intercurrent event (conservative definition).

^dRefers to an MI method in which HS-specific antibiotic use (HS-ABX) was treated as an intercurrent event.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Analysis Populations

[Table 10](#) provides a summary and the definitions of datasets and their applications in the BE HEARD I and II trials.

Table 10: Analysis Data Sets for BE HEARD I and BE HEARD II Studies

Population	Definition	Application
RS (ITT)	Study participants randomized into the study.	Used in all efficacy analyses and study population analyses.
SS	Study participants who received at least 1 full or partial dose of the drug under investigation.	Used for demographic, safety, and immunogenicity analyses.
FAS	Study participants who received at least 1 full or partial dose of the drug under investigation and had valid baseline and postbaseline measurements for abscess, inflammatory nodule, and draining tunnel counts.	Used in sensitivity analysis of primary end points and study population analyses.
AMS	Study participants who received at least 1 full or partial dose of bimekizumab.	Used for summaries of safety that included all data from the initial treatment period and the maintenance treatment period.
MS	Study participants who received at least 1 full or partial dose of bimekizumab in the maintenance treatment period.	Used in the study population and safety analyses during the maintenance treatment period.
PPS	Study participants in the FAS with no important protocol deviations for drug affecting the primary efficacy variable.	Drug-under-investigation protocol deviations were predefined, and study participants with drug-under-investigation protocol deviations were evaluated during ongoing data-cleaning meetings before unblinding of the data.

Population	Definition	Application
CFS	Study participants randomized into the study with no COVID-19 drug under investigation through week 16.	Used for sensitivity analyses of the primary efficacy end point.

AMS = active medication set; CFS = COVID-19-free set; FAS = full analysis set; ITT = intention to treat; MS = maintenance set; PPS = per-protocol set; RS = randomized set; SS = safety set.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Protocol Amendments

The original protocols for the BE HEARD I trial were amended 5 times and for the BE HEARD II trial were amended 4 times. [Table 11](#) presents the protocol amendments for both trials.

Table 11: Protocol Amendments in the BE HEARD I and BE HEARD II Trials

Protocol amendment	BE HEARD I	BE HEARD II
Protocol amendment 1	December 6, 2019 Occurred before study participants were enrolled.	December 6, 2019 No study participants were enrolled at the time of the amendment.
	The amendment clarified the wording of the exploratory biomarker objective, TB management, to reflect the correct screening terminology (i.e., eligible for study or not eligible for study).	
Protocol amendment 2	December 16, 2019 No study participants were enrolled at the time of the amendment.	December 16, 2019 No study participants were enrolled at the time of the amendment.
	Updates were made to the study discontinuation or withdrawal criteria for study participants with IBD.	
Protocol amendment 3	February 3, 2021 Approximately 162 study participants had been enrolled by the time of the amendment.	February 9, 2021 Approximately 300 study participants had been enrolled by the time of the amendment.
	Key changes to the amendment were similar in both trials. • The order of secondary efficacy end points was aligned for closed testing procedure. • Removal of 30% cap on enrolment for the baseline antibiotic therapy strata. • Aligned the final independent DMC charter and the DMC SAP for the planned unblinded futility analysis for the DMC. • Updates and clarifications were made to schedule of activities, inclusion criteria, exclusion criteria, and severe acute respiratory syndrome (i.e., necessary protocol revisions due to the COVID-19 pandemic). Necessary protocol revisions due to the COVID-19 pandemic. • Removal of depression as a safety topic of interest while maintaining collection of data to monitor for this potential effect. • Added lesion care section and updated wound care section. • Clarified and updated prohibited medications and associated washout periods. • Addition of specific infection-related investigational medicinal product interruption criterion.	
Protocol amendment 4	May 9, 2022 505 participants had been enrolled at the time of the amendment.	May 6, 2022 All participants had been enrolled at the time of the amendment.

Protocol amendment	BE HEARD I	BE HEARD II
	The purpose of amendment was to align with regulatory requirements. The amendment, which was similar in both trials, was as follows: • It was recommended that a threshold for clinically meaningful within-patient change be used to define treatment success to establish efficacy for skin pain in phase III studies with patients with moderate to severe HS. • Using established guidelines and analytical methods, the sponsor conducted analyses to determine the threshold for clinically meaningful within-patient change that was applied in the final analysis for a responder definition based on the HSSDD worst skin pain item score. • Using this definition, pain response status at week 16 was added as a secondary end point to the study. This change also resulted in an addition to the sample size section, including assumptions on response rates.	
Protocol amendment 5	September 27, 2022 505 participants had been enrolled at the time of the amendment. • The purpose of this substantial amendment was to remove the flare (secondary) end point from the statistical testing procedure. • The rationale for the amendment was the lack of unanimous consensus on the definition of HS flare, including the flare definition used in previous and ongoing clinical studies (outside of and independent of the BE HEARD I trial), the continued lack of published validation studies of a flare end point, and inconsistent data on the flare end point observed both within the bimekizumab program and in recently published data from another experimental HS treatment. • Flare was included in the “other” end point in the study.	No amendment

DMC = data-monitoring committee; HS = hidradenitis suppurativa; HSSDD = Hidradenitis Suppurativa Symptom Daily Diary; IBD = inflammatory bowel disease; SAP = statistical analysis plan; TB = tuberculosis.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Results

Patient Disposition

Patient disposition in the BE HEARD I and BE HEARD II trials in the initial treatment period and maintenance treatment period is presented in [Table 12](#) and [Table 13](#).

In the BE HEARD I trial, 778 patients were screened and 273 (35.1%) were excluded from the study. In the BE HEARD II trial, 726 patients were screened and 217 (29.9%) were excluded. In the BE HEARD I and II trials, 78% and 82%, respectively, of exclusions at screening were due to ineligibility.

In both the BE HEARD I and II trials, most of the randomized patients in each group completed the initial treatment periods (BE HEARD I trial: bimekizumab 320 mg every 2 weeks, 89.6%, placebo, 90.3%; BE HEARD II trial: bimekizumab 320 mg every 2 weeks, 90.0%, placebo, 93.2%). The frequency of study

discontinuation in the bimekizumab 320 mg every 2 weeks and placebo groups in the BE HEARD I trial were 9.3% and 9.7%, respectively, and in the BE HEARD II trial, 9.6% and 6.8%, respectively.

Most patients in both studies completed the maintenance treatment period; study discontinuation was reported for 25.7% of patients in the BE HEARD I trial and 16.4% of patients in the BE HEARD II trial.

Table 12: Patient Disposition (Initial Treatment Period, Randomized Set)

Patient disposition, n (%) Characteristic	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. (N = 289)	Placebo (N = 72)	BKZ 320 mg q.2.w. (N = 291)	Placebo (N = 74)
Total patients screened, n	778		726	
Started ITP, n (%)	286 (99.0)	72 (100)	290 (99.7)	74 (100)
Completed ITP, n (%)	259 (89.6)	65 (90.3)	262 (90.0)	69 (93.2)
Discontinued study during ITP, n (%)	27 (9.3)	7 (9.7)	28 (9.6)	5 (6.8)
Primary reason for study discontinuation, n (%)				
AE	7 (2.4)	1 (1.4)	9 (3.1)	1 (1.4)
Lack of efficacy	0	0	1 (0.3)	0
Protocol violation	2 (0.7)	0	1 (0.3)	1 (1.4)
Lost to follow-up	2 (0.7)	1 (1.4)	3 (1.0)	1 (1.4)
Consent withdrawn by study patient (not due to AE)	14 (4.8)	4 (5.6)	12 (4.1)	2 (2.7)
Other	2 (0.7)	1 (1.4)	2 (0.7)	0
Completed ITP but did not enter MTP, n (%)	1 (0.3)	0	1 (0.3)	0
Primary reason for study discontinuation, n (%)				
AE	0	0	NR	NR
Protocol violation	1 (0.3)	0	NR	NR
Consent withdrawn by study patient (not due to AE)	0	0	1 (0.3)	0

AE = adverse event; BKZ = bimekizumab; ITP = initial treatment period; NR = not reported; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 13: Patient Disposition (Maintenance Period, Randomized Set)

Characteristic	BKZ 320 mg q.2.w. or q.4.w. (N = 129)	Placebo/BKZ 320 mg q.2.w. (N = 65)	BKZ 320 mg q.2.w. or q.4.w. (N = 130)	Placebo/BKZ 320 mg q.2.w. (N = 69)
Started MTP, n (%)	129 (100)	65 (100)	130 (100)	69 (100)
Completed MTP, n (%)	104 (80.6)	44 (67.7)	107 (82.3)	61 (88.4)
Discontinued study during MTP, n (%)	25 (19.4)	21 (32.3)	23 (17.7)	8 (11.6)
Primary reason for study discontinuation, n (%)				
AE	5 (3.9)	9 (13.8)	6 (4.6)	0
Lack of efficacy	3 (2.3)	1 (1.5)	2 (1.5)	0
Protocol violation	1 (0.8)	1 (1.5)	2 (1.5)	0
Lost to follow-up	3 (2.3)	2 (3.1)	1 (0.8)	2 (2.9)
Consent withdrawn by study participant (not due to AE)	11 (8.5)	7 (10.8)	10 (7.7)	6 (8.7)
Other	2 (1.6)	1 (1.5)	2 (1.5)	0
Discontinued drug under investigation during MTP, n (%)	1 (0.8)	0	NR	NR

AE = adverse event; BKZ = bimekizumab; MTP = maintenance treatment period; NR = not reported; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Protocol Deviations

In both studies, the most common protocol deviations were the use of prohibited concomitant medication. In the BE HEARD I trial, total protocol deviations were similar in both groups (bimekizumab 320 mg every 2 weeks, 17.6%; placebo, 19.4%), and 81.2% of the patients overall had no important protocol deviations during the initial treatment period in the randomized set used for the primary analysis. In the BE HEARD II trial, 83.9% of patients overall had no important protocol deviations during the initial treatment period in the randomized set (16.8% in the bimekizumab 320 mg every 2 weeks group versus 12.2% for the placebo group). In both studies, the incidence of patients who were excluded from the per-protocol set analysis due to important protocol deviations during the initial treatment period was low (3.6% in the BE HEARD I trial and 0.8% in the BE HEARD II trial).

Baseline Characteristics

The baseline characteristics of all patients in the BE HEARD I (N = 505) and BE HEARD II (N = 509) trials outlined in [Table 14](#) were limited to those most relevant to this review or most likely to affect the outcomes or interpretation of the study results.

The baseline characteristics of the patients enrolled were similar between groups within the studies, and generally comparable across the trials. The mean age of patients in the BE HEARD I trial was 36.7 years (SD = 12.0 years) (36.9 years [SD = 12.4 years] in the bimekizumab 320 mg every 2 weeks group versus 36.4 years [SD = 12.4 years] in the placebo group) and 36.6 years (SD = 12.4 years) in the BE HEARD II trial (36.9 years [SD = 12.3 years] in the bimekizumab 320 mg every 2 weeks group versus 38.1 years

[SD = 13.2 years] in the placebo group). Overall, 63.0% of the patients enrolled in the BE HEARD I trial were female (60.9% in bimekizumab 320 mg every 2 weeks group versus 61.1% in the placebo group) as were 50.7% of the patients enrolled in the BE HEARD II trial (51.5% in the bimekizumab 320 mg every 2 weeks group versus 41.9% in the placebo group). Most study patients in both groups in the BE HEARD trials were Asian, Black, or white.

The overall mean duration of disease was 9.01 years in the BE HEARD I trial (8.51 years in the bimekizumab 320 mg every 2 weeks group versus 11.51 years in the placebo group) and 7.0 years in the BE HEARD II trial (7.35 years in the bimekizumab 320 mg every 2 weeks group versus 8.03 years in the placebo group). The proportion of patients with baseline Hurley stage II (derived) was 50.3% in the BE HEARD I trial (51.6% in bimekizumab 320 mg every 2 weeks group versus 47.2% in the placebo group) and 61.1% in the BE HEARD II trial (60.8% in the bimekizumab 320 mg every 2 weeks group versus 60.8% in the placebo group).

Table 14: Baseline Demographics and Disease Characteristics of Patients in BE HEARD I and BE HEARD II Studies (Randomized Set)

Characteristic	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. (N = 289)	Placebo (N = 72)	BKZ 320 mg q.2.w. (N = 291)	Placebo (N = 74)
Age (years)				
Mean (SD)	36.9 (12.4)	36.4 (12.4)	36.9 (12.3)	38.1 (13.2)
Median (range)	36.0 (18 to 72)	33.5 (18 to 65)	35.0 (18 to 71)	37.0 (20 to 69)
Sex, n (%)				
Female	176 (60.9)	44 (61.1)	150 (51.5)	31 (41.9)
Male	113 (39.1)	28 (38.9)	141 (48.5)	43 (58.1)
Weight (kg)				
Mean (SD)	97.23 (25.36)	94.62 (24.81)	95.41 (24.22)	100.28 (23.65)
Median (range)	95.40 (48.0 to 189.0)	88.20 (51.5 to 172.4)	91.90 (51.8 to 183.3)	95.50 (64.0 to 158.0)
BMI (kg/m²)				
Mean (SD)	33.36 (8.31)	32.36 (7.77)	32.01 (8.04)	33.81 (8.70)
Median (range)	32.44 (18.1 to 65.5)	30.91 (17.3 to 48.9)	30.56 (17.2 to 64.9)	31.46 (19.8 to 54.9)
Racial group, n (%)				
American Indian or Alaska Native	2 (0.7)	0	1 (0.3)	0
Asian	2 (0.7)	3 (4.2)	22 (7.6)	5 (6.8)
Black	41 (14.2)	8 (11.1)	22 (7.6)	5 (6.8)
White	233 (80.6)	55 (76.4)	232 (79.7)	64 (86.5)
Other	10 (3.5)	5 (6.9)	12 (4.1)	0
Missing	1 (0.3)	1 (1.4)	2 (0.7)	0

Characteristic	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. (N = 289)	Placebo (N = 72)	BKZ 320 mg q.2.w. (N = 291)	Placebo (N = 74)
Geographic region, n (%)				
Asia and Australia	27 (9.3)	6 (8.3)	22 (7.6)	5 (6.8)
Central and Eastern Europe	30 (10.4)	5 (6.9)	123 (42.3)	28 (37.8)
Western Europe	100 (34.6)	33 (45.8)	68 (23.4)	15 (20.3)
North America	132 (45.7)	28 (38.9)	78 (26.8)	26 (35.1)
Smoking status, n (%)				
Never	111 (38.4)	27 (37.5)	106 (36.4)	26 (35.1)
Current	127 (43.9)	37 (51.4)	134 (46.0)	38 (51.4)
Former	43 (14.9)	7 (9.7)	49 (16.8)	10 (13.5)
Missing	8 (2.8)	1 (1.4)	2 (0.7)	0
Duration of disease (years)				
Mean (SD)	8.51 (7.62)	11.51 (9.87)	7.35 (7.38)	8.03 (8.61)
Median (range)	5.73 (0.5 to 40.7)	8.74 (0.5 to 46.9)	4.87 (0.5 to 41.3)	4.81 (0.5 to 51.3)
Hs-CRP (mg/L)				
n	289	72	288	74
Mean (SD)	19.45 (27.88)	18.58 (21.89)	15.72 (22.28)	19.06 (30.07)
Median (range)	9.61 (0.2 to 177.3)	12.07 (0.3 to 106.3)	8.31 (0.1 to 151.6)	6.98 (0.4 to 167.5)
DLQI total score				
n	289	72	287	72
Mean (SD)	11.5 (6.6)	12.4 (8.0)	10.6 (6.5)	11.9 (6.1)
Median (range)	11.0 (0 to 30)	12.0 (1 to 30)	10.0 (0 to 28)	11.5 (1 to 29)
Hurley stage, n (%)				
II	159 (55.0)	40 (55.6)	187 (64.3)	47 (63.5)
III	130 (45.0)	32 (44.4)	104 (35.7)	27 (36.5)
Hurley stage (derived^a), n (%)				
II	149 (51.6)	34 (47.2)	177 (60.8)	45 (60.8)
III	140 (48.4)	38 (52.8)	114 (39.2)	29 (39.2)
HSSDD worst skin pain score				
n	289	72	248	61
Mean (SD)	5.49 (2.54)	5.96 (2.47)	5.33 (2.41)	4.96 (2.44)

Characteristic	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. (N = 289)	Placebo (N = 72)	BKZ 320 mg q.2.w. (N = 291)	Placebo (N = 74)
Median (range)	5.71 (0.0 to 10.0)	6.17 (0.0 to 10.0)	5.29 (0.0 to 10.0)	5.43 (0.0 to 8.3)
HiSQOL total score				
n	289	72	287	73
Mean (SD)	25.06 (12.95)	25.89 (14.82)	24.22 (12.85)	26.92 (13.44)
Median (range)	24.00 (0.0 to 62.0)	23.00 (1.0 to 59.0)	22.0 (0.0 to 66.0)	28.00 (2.0 to 54.0)
Antibiotic use at baseline, n (%)				
Yes	26 (9.0)	6 (8.3)	27 (9.3)	7 (9.5)
No	263 (91.0)	66 (91.7)	264 (90.7)	67 (90.5)
Prior biologic treatments, n (%)				
Any immunosuppressant biologic	77 (26.9)	20 (27.8)	44 (15.2)	10 (13.5)
Adalimumab	65 (22.7)	17 (23.6)	37 (12.8)	9 (12.2)
Infliximab	13 (4.5)	5 (6.9)	8 (2.8)	0
Guselkumab	6 (2.1)	1 (1.4)	3 (1.0)	0
Secukinumab	1 (0.3)	1 (1.4)	1 (0.3)	0
Ustekinumab	4 (1.4)	0	1 (0.3)	0
Risankizumab	NR	NR	0	1 (1.4)

BKZ = bimekizumab; BMI = body mass index; DLQI = Dermatology Life Quality Index; HiSQOL = Hidradenitis Suppurativa Quality of Life; HSSDD = Hidradenitis Suppurativa Symptom Daily Diary; hs-CRP = high-sensitivity C-reactive protein; NR = not reported; q.2.w. = every 2 weeks; SD = standard deviation.

Note: Racial categories used in the table are as reported in the original source and may not align with Canada's Drug Agency inclusive language guidelines.

*The derived Hurley stage for each participant was the worst overall Hurley stage derived from the Hurley stages recorded across all anatomic regions.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Concomitant antibiotic use at baseline was 8.9% in the BE HEARD I trial (9.0% in the bimekizumab 320 mg every 2 weeks group versus 8.3% in the placebo group) and 9.2% in the BE HEARD II trial (9.3% in the bimekizumab 320 mg every 2 weeks group versus 9.5% in the placebo group). The overall mean DLQI score was 12.0 in the BE HEARD I trial (11.5 in the bimekizumab 320 mg every 2 weeks group versus 12.4 in the placebo group) and 10.8 in the BE HEARD II trial (10.6 in the bimekizumab 320 mg every 2 weeks group versus 11.9 in the placebo group). Antibiotic use at baseline was 91.0% in the bimekizumab 320 mg every 2 weeks group versus 91.7% in the placebo group in the BE HEARD I trial, and 90.7% in the bimekizumab 320 mg every 2 weeks group versus 90.5% in the placebo group in the BE HEARD II trial.

Exposure to Study Treatments

In the initial treatment period (maximum of 112 days), the median duration of drug exposure was 112.0 days in both groups across the trials. In the maintenance treatment period (maximum of 224 days), the median duration of drug exposure across treatment groups ranged from 223.5 days in the bimekizumab 320 mg

every 2 weeks group in the BE HEARD II trial to 224.0 days in the bimekizumab 320 mg every 2 weeks group in the BE HEARD I trial and in the placebo groups in both trials.

Table 15: Patient Exposure in the Initial Treatment Period (Safety Set)

Exposure	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. (N = 286)	Placebo (N = 72)	BKZ 320 mg q.2.w. (N = 290)	Placebo (N = 74)
Duration of exposure (days), n				
Mean (SD)	106.2 (20.1)	105.9 (21.7)	106.8 (17.8)	108.3 (17.3)
Median	112.0	112.0	112.0	112.0
Range	11 to 144	9 to 132	1 to 116	1 to 115
Total duration of exposure (patient-years)	83.1	20.9	84.8	21.9
Total time at risk (patient-years)	87.2	21.9	88.2	22.6
Treatment adherence (%), n	286	72	290	74
Mean (SD)	96.3 (10.4)	97.1 (8.8)	97.0 (7.7)	98.6 (4.3)
Range	13 to 100	50 to 100	50 to 100	75 to 100
Adherence < 75%, n (%)	10 (3.5)	3 (4.2)	8 (2.8)	0
Adherence ≥ 75%, n (%)	276 (96.5)	69 (95.8)	282 (97.2)	74 (100)

BKZ = bimekizumab; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 16: Patient Exposure in the Maintenance Treatment Period (Safety Set)

Exposure	BKZ 320 mg q.2.w. or q.4.w. (N = 129)	Placebo/BKZ 320 mg q.2.w. (N = 65)	BKZ 320 mg q.2.w. or q.4.w. (N = 130)	Placebo/BKZ 320 mg q.2.w. (N = 69)
Duration of exposure (days), n				
Mean (SD)	196.9 (60.4)	187.7 (66.2)	199.8 (54.1)	214.2 (30.1)
Median	224.0	224.0	223.5	224.0
Range	11 to 302	14 to 249	15 to 231	84 to 231
Total duration of exposure (patient-years)	69.5	33.4	71.1	40.5
Total time at risk (patient-years)	77.1	39.2	78.3	43.2
Treatment adherence (%), n	129	65	130	69
Mean (SD)	94.5 (10.6)	95.2 (9.7)	96.4 (7.3)	97.4 (4.2)
Range	44 to 100	58 to 100	50 to 100	81 to 100
Adherence < 75%, n (%)	7 (5.4)	4 (6.2)	2 (1.5)	0

Exposure	BKZ 320 mg q.2.w. or q.4.w. (N = 129)	Placebo/BKZ 320 mg q.2.w. (N = 65)	BKZ 320 mg q.2.w. or q.4.w. (N = 130)	Placebo/BKZ 320 mg q.2.w. (N = 69)
Adherence $\geq$ 75%, n (%)	122 (94.6)	61 (93.8)	128 (98.5)	69 (100)

BKZ = bimekizumab; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Concomitant Medications, Cointerventions, and Rescue Therapy

Concomitant Medications and Cointerventions

BE HEARD I study: The use of concomitant medications in the initial treatment period was 87.8% in the bimekizumab 320 mg every 2 weeks group versus 83.3% in the placebo group in the initial treatment period. The most frequently reported concomitant medications were paracetamol (21.8%), tozinameran (19.2%), and ibuprofen (16.0%). In the maintenance treatment period, 89.1% of patients in the bimekizumab 320 mg every 2 weeks or every 4 weeks received concomitant medications versus 95.4% in the placebo or bimekizumab 320 mg every 2 weeks group. The most frequently reported concomitant medications were tozinameran (26.1%), paracetamol (25.0%), and ibuprofen (20.3%).

BE HEARD II study: The use of concomitant medications in the initial treatment period was 79.3% in the bimekizumab 320 mg every 2 weeks group versus 78.4% in the placebo group. The most frequently reported concomitant medications were tozinameran (13.0%), ibuprofen (11.5%), and paracetamol (10.7%). In the maintenance treatment period, the proportion of patients who received concomitant medications was 91.5% in the bimekizumab 320 mg every 2 weeks or every 4 weeks group versus 84.1% in the placebo or bimekizumab 320 mg every 2 weeks group. The most frequently reported concomitant medications were tozinameran (28.1%), ibuprofen (13.2%), and paracetamol (12.1%).

Rescue Therapy

BE HEARD I study: During the initial treatment period, the proportion of patients who received concomitant systemic antibiotic rescue medications (considered to be intercurrent events) was 17.0% in the bimekizumab 320 mg every 2 weeks group versus 20.8% in the placebo group. The most frequently reported concomitant systemic antibiotic rescue medications were amoxicillin trihydrate and clavulanate potassium (3.4%; also taken as amoxicillin [2.2%]) and doxycycline (2.0%). In the maintenance treatment period, the proportion of patients who received systemic antibiotic rescue medications was 34.1% in the bimekizumab 320 mg every 2 weeks or every 4 weeks group versus 46.2% in the placebo or bimekizumab 320 mg every 2 weeks group. The most frequently reported systemic antibiotic rescue medications were amoxicillin trihydrate clavulanate potassium (8.5%; also taken as amoxicillin [6.0%]) and amoxicillin clavulanic acid [0.7%]) and doxycycline (6.7%; also taken as doxycycline hydrochloride [0.2%]).

BE HEARD II study: In the initial treatment period, the proportion of patients who received concomitant systemic antibiotic rescue medications was 15.1% in the bimekizumab 320 mg every 2 weeks group versus 8.1% in the placebo group. The most frequently reported systemic antibiotic rescue medications were clindamycin (2.2%; also taken as clindamycin hydrochloride [0.6%]); amoxicillin (2.0%; also taken as amoxicillin trihydrate clavulanate potassium [2.0%]); and doxycycline (2.0%; also taken as doxycycline

hydrochloride [0.2%]). In the maintenance treatment period, the proportion of patients who received systemic antibiotic rescue medications was 32.3% in the bimekizumab 320 mg every 2 weeks or every 4 weeks group versus 21.7% in the pooled placebo or bimekizumab 320 mg every 2 weeks group. The most frequently reported systemic antibiotic rescue medications were doxycycline (5.6%; also taken as doxycycline hydrochloride [0.4%]); amoxicillin (3.2%; also taken as amoxicillin trihydrate clavulanate potassium [4.8%] and amoxicillin trihydrate [0.2%]); and clindamycin (3.2%; also taken as clindamycin hydrochloride [0.6%]).

Table 17: Concomitant Rescue Medications in at Least 2% of Study Patients in Any Treatment Group (Initial Treatment Period)

Medication, n (%)	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. (N = 289)	Placebo (N = 72)	BKZ 320 mg q.2.w. (N = 291)	Placebo (N = 74)
Randomized set, N	289	72	291	74
Patients requiring any concomitant systemic antibiotic rescue medication, n (%)	49 (17.0)	15 (20.8)	44 (15.1)	6 (8.1)
Anti-infectives for systemic use, n (%)	49 (17.0)	15 (20.8)	44 (15.1)	6 (8.1)
Safety set, N	286	72	290	74
Any rescue analgesic medications, n (%)	11 (3.8)	8 (11.1)	13 (4.5)	6 (8.1)
Musculoskeletal system, n (%)	7 (2.4)	2 (2.8)	6 (2.1)	3 (4.1)
Nervous system, n (%)	9 (3.1)	6 (8.3)	9 (3.1)	3 (4.1)

BKZ = bimekizumab; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 18: Concomitant Rescue Medications in at Least 2% of Study Patients in Any Treatment Group (Maintenance Treatment Period)

Medication, n (%)	BKZ 320 mg q.2.w. or q.4.w. (N = 129)	Placebo/BKZ 320 mg q.2.w. (N = 65)	BKZ 320 mg q.2.w. or q.4.w. (N = 130)	Placebo/BKZ 320 mg q.2.w. (N = 69)
Patients requiring any concomitant systemic antibiotic rescue medication	44 (34.1)	30 (46.2)	42 (32.3)	15 (21.7)
Anti-infectives for systemic use	44 (34.1)	30 (46.2)	42 (32.3)	15 (21.7)
Any rescue analgesic medications	9 (7.0)	10 (15.4)	11 (8.5)	6 (8.7)
Musculoskeletal system	6 (4.7)	4 (6.2)	8 (6.2)	3 (4.3)
Nervous system	5 (3.9)	7 (10.8)	8 (6.2)	3 (4.3)

BKZ = bimekizumab; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Efficacy

A summary of key efficacy results, including the HiSCR50 and HiSCR75 responder rates, flare rate, and change from baseline in DLQI total score and HiSQOL total score, from the initial treatment period (up to week 16) of the BE HEARD I and BE HEARD II trials is provided in [Table 19](#). Key results from the maintenance treatment period (up to week 48) are summarized in [Table 20](#). The results for HSSDD worst skin pain score response rate were not collected and are thus unavailable at week 48. Only week 48 data from the bimekizumab 320 mg every 2 weeks or every 4 weeks groups are provided here as this is the only group that received treatment that aligned with the approved dosing. Further, the results up to week 48 were not intended to provide comparative data.

Disease Severity

HiSCR50 Responder Rate

The primary efficacy end point for the BE HEARD I and II trials was the HiSCR50 responder rate at week 16 ([Table 19](#)).

BE HEARD I study: The HiSCR50 responder rate (adjusted for intercurrent events and missing information imputed) at week 16 was 44.8% (95% CI, 35.8% to 53.8%) in the pooled bimekizumab 320 mg every 2 weeks group versus 26.7% (95% CI, 15.0% to 38.4%) in the placebo group (OR = 2.23; 97.5% CI, 1.16 to 4.31; P = 0.006 [tested at alpha = 0.025]). The between-group difference was 18.15% (95% CI, 6.31% to 29.98%) in favour of bimekizumab.

BE HEARD II study: The HiSCR50 responder rate (adjusted for intercurrent events and missing information imputed) at week 16 was 50.3% (95% CI, 41.5% to 59.0%) in the pooled bimekizumab 320 mg every 2 weeks group versus 30.7% (95% CI, 18.6% to 42.7%) in the placebo group (OR = 2.29; 97.5% CI, 1.22 to 4.29; P = 0.003 [tested at alpha = 0.025]). The between-group difference was 19.61% (95% CI, 7.50% to 31.72%) in favour of bimekizumab.

In both the BE HEARD I and BE HEARD II trials, sensitivity analyses for the HiSCR50 responder rate were performed to account for alternative methods for differing definitions of intercurrent events and missing data or with additional analysis sets, as described in the Statistical Analysis section of this report. In both trials, all sensitivity analyses were supportive of the results of the primary analysis, except for the tipping-point analysis in the worst-case scenarios.

Responder rates for HiSCR50 up to week 48 were reported in both trials as exploratory end points.

BE HEARD I study: Responder rates at week 48 were 40.2% (95% CI, 31.7% to 48.7%) in the pooled bimekizumab 320 mg every 2 weeks followed by every 4 weeks group and 31.7% (95% CI, 20.3% to 43.1%) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

BE HEARD II study: Responder rates at week 48 were 44.5% (95% CI, 36.0% to 53.0%) in the pooled bimekizumab 320 mg every 2 weeks followed by every 4 weeks group and 55.8% (95% CI, 44.0% to 67.6%) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

HiSCR75 Responder Rate

HiSCR75 at week 16 was assessed as a ranked secondary outcome in the BE HEARD I and II trials ([Table 19](#)).

BE HEARD I study: The HiSCR75 responder rate (adjusted for intercurrent events and missing information imputed) at week 16 was 35.7% (95% CI, 27.0% to 44.4%) in the pooled bimekizumab 320 mg every 2 weeks group versus 20.3% (95% CI, 9.4% to 31.2%) in the placebo group (OR = 2.18; 97.5% CI, 1.02 to 4.64; P = 0.021 [tested at alpha = 0.025]). The between-group difference was 15.35% (95% CI, 3.71% to 27.00%) in favour of bimekizumab.

BE HEARD II study: The HiSCR75 responder rate (adjusted for intercurrent events and missing information imputed) at week 16 was 36.8% (95% CI, 28.4% to 45.2%) in the pooled bimekizumab 320 mg every 2 weeks group versus 16.3% (95% CI, 6.8% to 25.7%) in the placebo group (OR = 3.01; 97.5% CI, 1.37 to 6.58; P = 0.002 [tested at alpha = 0.025]). The between-group difference was 20.57% (95% CI, 9.90% to 31.26%) in favour of bimekizumab.

Responder rates for HiSCR75 up to week 48 were reported in both trials as exploratory end points.

BE HEARD I study: Responder rates at week 48 were 28.1% (95% CI, 20.2% to 35.9%) in the pooled bimekizumab 320 mg every 2 weeks followed by every 4 weeks group and 26.6% (95% CI, 15.9% to 37.3%) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

BE HEARD II study: Responder rates at week 48 were 32.8% (95% CI, 24.8% to 40.8%) in the pooled bimekizumab 320 mg every 2 weeks followed by every 4 weeks group and 48.5% (95% CI, 36.7% to 60.4%) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

Disease Worsening

Flare

In the BE HEARD I trial, flare rate by week 16 was analyzed descriptively as a nonranked secondary end point; in the BE HEARD II trial, flare by week 16 was tested as a ranked secondary end point, but was not found to be significantly different, terminating hierarchical testing. In both trials, flare by week 48 was an exploratory outcome and only presented descriptively ([Table 19](#)).

BE HEARD I study: By week 16, 28.5% (95% CI, 23.2% to 33.9%) of patients in the pooled bimekizumab 320 mg every 2 weeks group reported a flare compared with 47.8% (95% CI, 36.1% to 59.4%) of patients in the placebo group. By week 48, 55.9% (95% CI, 47.6% to 64.3%) of patients in the pooled bimekizumab 320 mg every 2 weeks followed by every 4 weeks group reported a flare compared with 69.9% (95% CI, 59.0% to 80.7%) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

BE HEARD II study: By week 16, 28.8% (95% CI, 23.5% to 34.1%) of patients in the pooled bimekizumab 320 mg every 2 weeks group reported a flare compared with 28.0% (95% CI, 17.6% to 38.4%) of patients in the placebo group (OR = 1.050; 97.5% CI, 0.541 to 2.041; P = 0.868 [tested at alpha = 0.025]). By week 48, 51.2% (95% CI, 42.9% to 59.4%) in the pooled bimekizumab 320 mg every 2 weeks followed by every

4 weeks group reported a flare compared with 37.9% (95% CI, 26.6% to 49.2%) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

Health-Related Quality of Life

Change From Baseline in DLQI Total Score

Change from baseline in DLQI total score at week 16 was included as a ranked secondary outcome in both trials ([Table 19](#)). An MID of 4 points was adopted by the sponsor as a clinically meaningful threshold, based on evidence from prior studies on other skin conditions (but not HS).

BE HEARD I study: The LS mean change from baseline to week 16 was -5.21 (95% CI, -6.14 to -4.29) in the pooled bimekizumab 320 mg every 2 weeks group and -2.53 (95% CI, -4.07 to -0.996) in the placebo group. The between-group treatment difference was -2.68 (97.5% CI, -4.39 to -0.97 ; $P < 0.001$ [tested at $\alpha = 0.025$]), in favour of bimekizumab.

BE HEARD II study: The LS mean change from baseline was -4.69 (95% CI, -5.49 to -3.897) in the pooled bimekizumab 320 mg every 2 weeks group versus -2.38 (95% CI, -3.64 to -1.13) in the placebo group. The between-group difference was -2.31 (97.5% CI, -3.71 to -0.91). Statistical significance could not be interpreted due to a prior nonsignificant result in the statistical testing hierarchy.

The change from baseline in DLQI total score was reported up to week 48 in both trials. In the pooled bimekizumab every 2 weeks or every 4 weeks group, mean change from baseline at week 48 was -5.0 (SE = 0.6) in the BE HEARD I trial and -5.4 (SE = 0.6) in the BE HEARD II trial. In the placebo followed by bimekizumab every 2 weeks group, mean change from baseline was -6.1 (SE = 1.2) in the BE HEARD I trial and -6.7 (SE = 0.8) in the BE HEARD II trial.

Change From Baseline in HiSQOL Total Score

Change from baseline in HiSQOL total score up to week 48 was assessed as an exploratory outcome in both trials. A clinically meaningful change in HiSQOL was defined as a minimum 20-point reduction from baseline score.

BE HEARD I study: By week 16, the mean change from baseline in HiSQOL total score was -11.1 (SE = 1.1) in the pooled bimekizumab 320 mg every 2 weeks group and -5.2 (SE = 1.6) in the placebo group. By week 48, the mean change from baseline was -12.3 (SE = 1.3) in the pooled bimekizumab 320 mg every 2 weeks followed by every 4 weeks group and -13.0 (SE = 2.2) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

BE HEARD II study: By week 16, the mean change from baseline in HiSQOL total score was -10.3 (SE = 1.0) in the pooled bimekizumab 320 mg every 2 weeks group and -5.8 (SE = 1.3) in the placebo group. By week 48, the mean change from baseline was -13.4 (SE = 1.2) in the pooled bimekizumab 320 mg every 2 weeks followed by every 4 weeks group and -15.6 (SE = 1.6) in the placebo followed by bimekizumab 320 mg every 2 weeks group.

Symptoms

Worst Skin Pain Responder Rate, Based on Clinically Meaningful Change in the HSSDD

The HSSDD is a patient-reported outcome capturing patients' experiences of pain via 5 domains. At week 16, the HSSDD worst skin pain responder rate was assessed as a ranked secondary outcome, based on a clinically meaningful change in the worst skin pain item among study participants who had a score of 3 or more at baseline ([Table 19](#)). A clinically meaningful change in the HSSDD worst skin pain score was defined as a minimum 3-point reduction from baseline score, based on weekly averages.⁴⁹

Table 19: Key Efficacy Outcomes at Week 16 (Initial Treatment Period, Randomized Set)

Variable	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. (N = 289)	Placebo (N = 72)	BKZ 320 mg q.2.w. (N = 291)	Placebo (N = 74)
HiSCR50 responder rate ^a				
Number of responders/ number of patients with nonmissing data	151/257	24/65	164/265	24/70
Observed responder rate, % (95% CI)	47.8 (41.8 to 53.7)	28.7 (18.1 to 39.3)	52.0 (46.1 to 57.8)	32.2 (21.4 to 42.9)
Adjusted responder rate, % (95% CI)	44.8 (35.8 to 53.8)	26.7 (15.0 to 38.4)	50.3 (41.5 to 59.0)	30.7 (18.6 to 42.7)
Treatment group difference vs. placebo (95% CI)	18.145 (6.313 to 29.977)		19.610 (7.501 to 31.719)	
Odds ratio vs. placebo (97.5% CI)	2.234 (1.159 to 4.307)		2.287 (1.220 to 4.291)	
P value	0.006		0.003	
HiSCR75 responder rate ^a				
Number of responders/ number of patients with nonmissing data	107/257	13/65	112/265	12/70
Observed responder rate, % (95% CI)	33.4 (27.8 to 39.1)	18.4 (9.3 to 27.5)	35.7 (30.1 to 41.3)	15.6 (7.2 to 24.0)
Adjusted responder rate, % (95% CI)	35.7 (27.0 to 44.4)	20.3 (9.4 to 31.2)	36.8 (28.4 to 45.2)	16.3 (6.8 to 25.7)
Treatment group difference vs. placebo (95% CI)	15.352 (3.710 to 26.995)		20.574 (9.888 to 31.260)	
Odds ratio vs. placebo (97.5% CI)	2.175 (1.021 to 4.635)		3.007 (1.374 to 6.581)	
P value	0.021		0.002	
Flare by week 16 ^b				
Number of patients with a flare by week 16/	34/284	25/71	42/288	15/73

	BE HEARD I		BE HEARD II	
Variable	BKZ 320 mg q.2.w. (N = 289)	Placebo (N = 72)	BKZ 320 mg q.2.w. (N = 291)	Placebo (N = 74)
number of patients with nonmissing data				
Observed flare rate, % (95% CI)	28.5 (23.2 to 33.9)	47.8 (36.1 to 59.4)	28.8 (23.5 to 34.1)	28.0 (17.6 to 38.4)
Adjusted flare rate, % (95% CI)	NA	NA	27.4 (19.5 to 35.2)	26.4 (14.7 to 38.1)
Treatment group difference vs. placebo (95% CI)	NR		0.960 (−10.370 to 12.289)	
Odds ratio vs. placebo (97.5% CI)	NR		1.050 (0.541 to 2.041)	
P value	NR		0.868	
Absolute change from baseline in DLQI total score ^c				
Number of patients contributing to analysis, n	250	64	264	68
Mean (SD)	−5.01 (6.05)	−2.67 (6.15)	−4.49 (5.64)	−3.07 (5.03)
LS mean change (95% CI)	−5.214 (−6.139 to −4.289)	−2.532 (−4.069 to −0.996)	−4.692 (−5.486 to −3.897)	−2.382 (−3.636 to −1.128)
Treatment group difference vs. placebo (97.5% CI)	−2.682 (−4.394 to −0.970)		−2.309 (−3.705 to −0.914)	
P value	< 0.001		< 0.001 ^d	
Change from baseline in HiSQOL total score				
Number of patients contributing to analysis, n	146	72	146	74
Number of responders/ number of patients with nonmissing data	128/131	65/65	134/134	70/70
Change from baseline, mean (SE)	−11.1 (1.1)	−5.2 (1.6)	−10.3 (1.0)	−5.8 (1.3)
HSSDD worst skin pain score response rate ^e				
Number of participants with a score ≥ 3 at baseline, n	190	46	209	49
Number of responders/ number of patients with nonmissing data	55/138	4/26	62/163	4/42
Observed responder rate, % (95% CI)	32.3 (25.1 to 39.5)	15.0 (3.6 to 26.5)	31.8 (25.1 to 38.4)	10.9 (1.7 to 20.1)
Adjusted responder rate, % (95% CI) ^a	35.4 (24.1 to 46.6)	16.7 (3.6 to 29.8)	29.8 (18.9 to 40.7)	10.2 (0.7 to 19.7)

Variable	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. (N = 289)	Placebo (N = 72)	BKZ 320 mg q.2.w. (N = 291)	Placebo (N = 74)
Treatment group difference vs. placebo (95% CI)	18.66 (3.32 to 33.99)		19.57 (7.495 to 31.64)	
Odds ratio vs. placebo (97.5% CI)	2.757 (0.909 to 8.364)		3.756 (1.189 to 11.867)	
P value	0.041		0.010 ^d	

BKZ = bimekizumab; CI = confidence interval; DLQI = Dermatology Life Quality Index; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HiSQOL = Hidradenitis Suppurativa Quality of Life; HSSDD = Hidradenitis Suppurativa Symptom Daily Diary; LS = least squares; MCMC = Markov Chain Monte Carlo; MI = multiple imputation; NA = not applicable; NR = not reported; q.2.w. = every 2 weeks; SD = standard deviation; SE = standard error; vs. = versus.

^aIntermittent missing data were imputed using MI with MCMC method followed by monotone regression for monotone missing data. Lesion counts were imputed and then dichotomized to obtain the response status. Patients who experienced an intercurrent event were treated as nonresponders following the intercurrent event.

^bIntermittent missing data were imputed using MI with MCMC method followed by monotone regression for monotone missing data. Lesion counts were imputed and then dichotomized to obtain the response status. Participants who experienced an intercurrent event were treated as having experienced a flare following the intercurrent event.

^cIntermittent missing data were imputed using MI with MCMC method followed by monotone regression for monotone missing data. Participants who experienced an intercurrent event were treated as missing following the intercurrent event and imputed using the MI method for missing data.

^dP value corresponds to an end point tested after a prior hierarchical failure or not included in the statistical hierarchy.

^eIntermittent missing data were imputed using MI with MCMC method followed by monotone regression for monotone missing data. Weekly pain scores were imputed and then dichotomized to obtain the response status. Participants who experienced an intercurrent event were treated as nonresponders following the intercurrent event.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

BE HEARD I study: The adjusted responder rate was 35.4% (95% CI, 24.1% to 46.6%) in the pooled bimekizumab 320 mg every 2 weeks group versus 16.7% (95% CI, 3.6% to 29.8%) in the placebo group (OR = 2.76; 97.5% CI, 0.91 to 8.36; P = 0.041 [tested at alpha = 0.025]). The between-group difference was 18.66% (95% CI, 3.32% to 33.99%).

BE HEARD II study: The adjusted responder rate was 29.8% (95% CI, 18.9% to 40.7%) in the pooled bimekizumab 320 mg every 2 weeks group versus 10.2% (95% CI, 0.7% to 19.7%) in the placebo group (OR = 3.76; 97.5% CI, 1.189 to 11.867). The between-group difference was 19.57% (95% CI, 7.50% to 31.64%). Statistical significance could not be interpreted due to a prior nonsignificant result in the statistical testing hierarchy.

The HSSDD worst skin pain score response based on clinically meaningful change at week 48 was not assessed in either of the trials.

Key efficacy results, including the HiSCR50 and HiSCR75 responder rates, flare rate, and change from baseline in DLQI total score and HiSQOL total score during the maintenance treatment period (up to week 48), are summarized in [Table 20](#). The results for HSSDD worst skin pain score response rate were not collected and are thus unavailable at week 48. Only data for the bimekizumab 320 mg every 2 weeks or every 4 weeks treatment group are provided here to align with the approved dosing. Further, the results up to week 48 were not intended to provide comparative data.

Table 20: Key Efficacy Outcomes in BE HEARD I and BE HEARD II Studies at Week 48 (Maintenance Treatment Period, Randomized Set)

Outcome	BE HEARD I BKZ 320 mg q.2.w. or q.4.w. (N = 146)	BE HEARD II BKZ 320 mg q.2.w. or q.4.w. (N = 146)
HiSCR50 responder rate^a by week 48		
Number of responders/number of patients with nonmissing data at week 16, (%)	83/104 (79.8)	87/107 (81.3)
Week 48 responder rate, % (95% CI)	40.2 (31.7 to 48.7)	44.5 (36.0 to 53.0)
HiSCR75 responder rate by week 48		
Number of responders/number of patients with nonmissing data at week 16, (%)	58/104 (55.8)	69/107 (64.5)
Week 48 responder rate, % (95% CI)	28.1 (20.2 to 35.9)	32.8 (24.8 to 40.8)
Flare rate by week 48		
Number of responders/number of patients with nonmissing data at week 16, (%)	27/144 (18.8)	26/145 (17.9)
Flare rate by week 48, % (95% CI)	55.9 (47.6 to 64.3)	51.2 (42.9 to 59.4)
Change from baseline in DLQI total score^b		
Baseline, mean (SE)	11.0 (0.6)	10.5 (0.6)
Change from baseline at week 48, mean (SE)	−5.0 (0.6)	−5.4 (0.6)
Change from baseline in HiSQOL total score		
Number of responders/number of patients with nonmissing data at week 16, (%)	103/104 (99.0)	106/107 (99.1)
Change from baseline at week 48, mean (SE)	−12.3 (1.3)	−13.4 (1.2)

BKZ = bimekizumab; CI = confidence interval; DLQI = Dermatology Life Quality Index; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HiSQOL = Hidradenitis Suppurativa Quality of Life; MCMC = Markov Chain Monte Carlo; MI = multiple imputation; OC = observed case; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SE = standard error.

Note: For the number of patients with a nonmissing measurement at week 16, percentages were calculated accordingly (i.e., where data recorded after an intercurrent event were included as recorded).

^aIntermittent missing data are imputed using MI with MCMC method followed by monotone regression for monotone missing data. Lesion counts were imputed and then dichotomized to obtain the response status. Participants who experienced an intercurrent event were treated as nonresponders following the intercurrent event.

^bIntermittent missing data are imputed using MI with MCMC method followed by monotone regression for monotone missing data. Participants who experienced an intercurrent event were treated as missing following the intercurrent event and imputed using the MI method for missing data.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Harms

In the BE HEARD I and II trials, safety analyses included all AEs, most frequently reported AEs, SAEs, AEs leading to study withdrawal, and deaths due to AEs. Both the BE HEARD I and II trials evaluated safety during the initial and maintenance treatment periods. In addition, a safety evaluation was conducted during the overall treatment period (initial treatment period and maintenance treatment period) with the active medication set, which included all patients who received at least 1 full or partial dose of bimekizumab. Summaries of harms in the initial treatment period and the overall treatment period are provided in [Table 21](#)

and [Table 22](#), respectively. A summary of harms during the maintenance treatment period is available in [Appendix 1](#).

Adverse Events

In the initial treatment period of the BE HEARD I trial, 67.1% of patients in the bimekizumab 320 mg every 2 weeks group and 66.7% of patients in the placebo group reported at least 1 AE. In the BE HEARD II trial, 64.5% of patients in the bimekizumab 320 mg every 2 weeks group and 56.8% in the placebo group reported AEs in the initial treatment period. In the BE HEARD I trial, the most frequently reported AEs ($\geq 5\%$ of patients) in the bimekizumab 320 mg every 2 weeks group versus the placebo group were hidradenitis (6.6% versus 13.9%, respectively), back pain (2.4% versus 8.3%, respectively), and headache (7.7% versus 4.2%, respectively). In the BE HEARD II trial, the most common AEs ($\geq 5\%$ of patients) reported in the bimekizumab 320 mg every 2 weeks group versus the placebo group were diarrhea (6.2% versus 8.1%, respectively), headache (6.2% versus 9.5%, respectively), and hidradenitis (8.6% versus 6.8%, respectively).

In the overall treatment period of the BE HEARD I trial, 85.5% of AEs were reported in the bimekizumab 320 mg every 2 weeks followed by every 4 weeks group versus 92.3% in the placebo or bimekizumab 320 mg every 2 weeks group. The most common AEs ($\geq 5\%$ of patients) reported in the bimekizumab 320 mg every 2 weeks or every 4 weeks group versus the placebo group included diarrhea (8.3% versus 10.8%, respectively), oral candidiasis (11.0% versus 4.6%, respectively), folliculitis (7.6% versus 3.1%, respectively), nasopharyngitis (8.3% versus 9.2%, respectively), coronavirus infection (15.9% versus 16.9%, respectively), headache (11.0% versus 10.8%, respectively), hidradenitis (18.6% versus 29.2%, respectively).

In the overall treatment period of the BE HEARD II trial, 87.7% of AEs were reported in the bimekizumab 320 mg every 2 weeks or every 4 weeks group and 76.8% in the placebo or bimekizumab 320 mg every 2 weeks group. The most common AEs ($\geq 5\%$ of patients) reported in the bimekizumab 320 mg every 2 weeks or every 4 weeks group versus the placebo group included hidradenitis (21.2% versus 14.5%, respectively), headache (9.6% versus 13.0%, respectively), coronavirus infection (10.3% versus 5.8%, respectively), oral candidiasis (17.1% versus 4.3%, respectively), and diarrhea (11.0% versus 10.1%, respectively).

Serious Adverse Events

In the initial treatment period, the proportion of SAEs reported in the pooled bimekizumab 320 mg every 2 weeks group was 2.1% in the BE HEARD I trial and 3.1% in the BE HEARD II trial. No SAEs were reported in the placebo group of either study.

In the overall treatment period of the BE HEARD I trial, the proportion of SAEs reported in the placebo and bimekizumab 320 mg every 2 weeks group was 9.2% compared to 5.5% in the bimekizumab 320 mg every 2 weeks followed by every 4 weeks group. In the BE HEARD II trial, the proportion of SAEs reported in the placebo or bimekizumab 320 mg every 2 weeks group was 3.4% compared to 2.9% in the bimekizumab 320 mg every 2 weeks followed by every 4 weeks group.

Withdrawals Due to Adverse Events

In the initial treatment period of the BE HEARD I trial, 3.5% of patients in the pooled bimekizumab 320 mg every 2 weeks group and 1.4% of patients in the placebo group discontinued study treatment due to AEs. In the BE HEARD II trial, no patients in the placebo group and 4.1% of patients in the bimekizumab 320 mg every 2 weeks group discontinued study treatment due to AEs.

In the overall treatment period, the incidence of AEs leading to BE HEARD I trial discontinuation was 6.9% in the bimekizumab 320 mg every 2 weeks followed by every 4 weeks group and 13.8% in the placebo or bimekizumab 320 mg every 2 weeks group. In the BE HEARD II trial, the incidence of AEs leading to discontinuation was 6.8% in the bimekizumab 320 mg every 2 weeks followed by every 4 weeks group, and 0% in the placebo or bimekizumab 320 mg every 2 weeks group.

Mortality

No deaths were reported in either study.

Notable Harms

Oral candidiasis was a notable harm identified by the clinical experts consulted for this review. In the initial treatment period (the safety set) of both the BE HEARD I and II trials, oral candidiasis was reported in 5.9% and 8.3%, respectively, of patients in the pooled bimekizumab 320 mg every 2 weeks groups. No oral candidiasis was reported in the placebo groups of either trial.

In the overall treatment period (active medication set), all the groups that received bimekizumab reported candida infections, with most occurrences being oral candidiasis. In the BE HEARD I trial, 11.0% of the bimekizumab 320 mg every 2 weeks or every 4 weeks group and 4.6% of the placebo or bimekizumab 320 mg every 2 weeks group reported oral candidiasis. In the BE HEARD II trial, 17.1% of the bimekizumab 320 mg every 2 weeks or every 4 weeks group and 4.3% of the placebo or bimekizumab 320 mg every 2 weeks group reported oral candidiasis infections.

Table 21: Summary of Harms Results From Studies Included in the Systematic Review (Initial Treatment Period, Safety Set)

Adverse events	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. (N = 286)	Placebo (N = 72)	BKZ 320 mg q.2.w. (N = 290)	Placebo (N = 74)
Most common AEs^a, n (%)				
Patients with ≥ 1 AE	192 (67.1)	48 (66.7)	187 (64.5)	42 (56.8)
Gastrointestinal disorders	49 (17.1)	9 (12.5)	53 (18.3)	11 (14.9)
Diarrhea	18 (6.3)	1 (1.4)	18 (6.2)	6 (8.1)
Infections and infestations	98 (34.3)	18 (25.0)	95 (32.8)	12 (16.2)
Oral candidiasis	17 (5.9)	0	24 (8.3)	0
Musculoskeletal and connective tissue disorders	23 (8.0)	12 (16.7)	NR	NR

Adverse events	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. (N = 286)	Placebo (N = 72)	BKZ 320 mg q.2.w. (N = 290)	Placebo (N = 74)
Back pain	7 (2.4)	6 (8.3)	NR	NR
Nervous system disorders	32 (11.2)	4 (5.6)	22 (7.6)	9 (12.2)
Headache	22 (7.7)	3 (4.2)	18 (6.2)	7 (9.5)
Skin and subcutaneous tissue disorders	66 (23.1)	18 (25.0)	82 (28.3)	8 (10.8)
Hidradenitis	19 (6.6)	10 (13.9)	25 (8.6)	5 (6.8)
Serious adverse events, n (%)				
Patients with ≥ 1 SAE	6 (2.1)	0	9 (3.1)	0
Patients who stopped treatment due to AEs, n (%)				
Patients who stopped treatment due to an AE	10 (3.5)	1 (1.4)	12 (4.1)	0
Deaths, n (%)				
Patients who died	0	0	0	0
AEs of special interest, n (%)				
Candida infections	22 (7.7)	0	26 (9.0)	0
Fungal infections	34 (11.9)	1 (1.4)	41 (14.1)	0
Hypersensitivity reactions	30 (10.5)	4 (5.6)	32 (11.0)	1 (1.4)
Injection site reactions	14 (4.9)	1 (1.4)	22 (7.6)	1 (1.4)
Hepatic events	8 (2.8)	4 (5.6)	6 (2.1)	0

AE = adverse event; BKZ = bimekizumab; NR = not reported; q.2.w. = every 2 weeks; SAE = serious adverse event.

^aAEs reported by at least 5% of patients in any treatment group.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 22: Summary of Harms Data Results From Studies Included in the Systematic Review (Overall Treatment Period, Active Medication Set)

Adverse events	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. or q.4.w. (N = 145)	Placebo/BKZ 320 mg q.2.w. (N = 65)	BKZ 320 mg q.2.w. or q.4.w. (N = 146)	Placebo/BKZ 320 mg q.2.w. (N = 69)
Most common AEs^a, n (%)				
Patients with ≥ 1 AE	124 (85.5)	60 (92.3)	128 (87.7)	53 (76.8)
Gastrointestinal disorders	44 (30.3)	19 (29.2)	42 (28.8)	18 (26.1)
Diarrhea	12 (8.3)	7 (10.8)	16 (11.0)	7 (10.1)
Abdominal pain	6 (4.1)	4 (6.2)	NR	NR
General disorders and administration site conditions	24 (16.6)	10 (15.4)	34 (23.3)	11 (15.9)

Adverse events	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. or q.4.w. (N = 145)	Placebo/BKZ 320 mg q.2.w. (N = 65)	BKZ 320 mg q.2.w. or q.4.w. (N = 146)	Placebo/BKZ 320 mg q.2.w. (N = 69)
Pyrexia	8 (5.5)	3 (4.6)	7 (4.8)	2 (2.9)
Fatigue	NR	NR	9 (6.2)	1 (1.4)
Infections and infestations	89 (61.4)	43 (66.2)	85 (58.2)	34 (49.3)
Oral candidiasis	16 (11.0)	3 (4.6)	25 (17.1)	3 (4.3)
Influenza	2 (1.4)	5 (7.7)	NR	NR
Folliculitis	11 (7.6)	2 (3.1)	9 (6.2)	2 (2.9)
Nasopharyngitis	12 (8.3)	6 (9.2)	11 (7.5)	2 (2.9)
Upper respiratory tract infection	10 (6.9)	2 (3.1)	6 (4.1)	5 (7.2)
Urinary tract infection	9 (6.2)	5 (7.7)	6 (4.1)	5 (7.2)
Coronavirus infection	23 (15.9)	11 (16.9)	15 (10.3)	4 (5.8)
Investigations	22 (15.2)	19 (29.2)	NR	NR
Aspartate aminotransferase increased	1 (0.7)	4 (6.2)	NR	NR
Psychiatric evaluation abnormal	4 (2.8)	5 (7.7)	NR	NR
Musculoskeletal and connective tissue disorders	23 (15.9)	15 (23.1)	NR	NR
Back pain	7 (4.8)	6 (9.2)	NR	NR
Nervous system disorders	22 (15.2)	11 (16.9)	21 (14.4)	13 (18.8)
Headache	16 (11.0)	7 (10.8)	14 (9.6)	9 (13.0)
Respiratory, thoracic, and mediastinal disorders	14 (9.7)	6 (9.2)	NR	NR
Oropharyngeal pain	6 (4.1)	4 (6.2)	NR	NR
Skin and subcutaneous tissue disorders	63 (43.4)	37 (56.9)	65 (44.5)	25 (36.2)
Hidradenitis	27 (18.6)	19 (29.2)	31 (21.2)	10 (14.5)
Eczema	8 (5.5)	3 (4.6)	13 (8.9)	4 (5.8)
Intertrigo	7 (4.8)	2 (3.1)	NR	NR
Seborrheic dermatitis	11 (7.6)	3 (4.6)	NR	NR
Pruritus	3 (2.1)	3 (4.6)	8 (5.5)	2 (2.9)
Serious adverse events, n (%)				
Patients with ≥ 1 SAE	8 (5.5)	6 (9.2)	5 (3.4)	2 (2.9)
Pregnancy, puerperium, and perinatal conditions	2 (1.4)	0	0	0

Adverse events	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. or q.4.w. (N = 145)	Placebo/BKZ 320 mg q.2.w. (N = 65)	BKZ 320 mg q.2.w. or q.4.w. (N = 146)	Placebo/BKZ 320 mg q.2.w. (N = 69)
Patients who stopped treatment due to AEs, n (%)				
Patients who stopped treatment due to an AE	10 (6.9)	9 (13.8)	10 (6.8)	0
Gastrointestinal disorders	1 (0.7)	1 (1.5)	2 (1.4)	0
Infections and infestations	4 (2.8)	3 (4.6)	3 (2.1)	0
Oral candidiasis	3 (2.1)	1 (1.5)	1 (0.7)	0
Investigations	0	2 (3.1)	1 (0.7)	0
Psychiatric evaluation abnormal	0	2 (3.1)	1 (0.7)	0
Skin and subcutaneous tissue disorders	1 (0.7)	4 (6.2)	6 (4.1)	0
Hidradenitis	0	3 (4.6)	4 (2.7)	0
Deaths, n (%)				
Patients who died	0	0	0	0
AEs of special interest, n (%)				
Candida infections	21 (14.5)	4 (6.2)	29 (19.9)	4 (5.8)
Serious infections	3 (2.1)	1 (1.5)	1 (0.7)	1 (1.4)
Opportunistic infections	3 (2.1)	1 (1.5)	1 (0.7)	0
Fungal infections	32 (22.1)	12 (18.5)	39 (26.7)	10 (14.5)
Hypersensitivity reactions	30 (20.7)	15 (23.1)	28 (19.2)	10 (14.5)
Injection site reactions	8 (5.5)	2 (3.1)	11 (7.5)	2 (2.9)
Hepatic events	7 (4.8)	7 (10.8)	7 (4.8)	2 (2.9)

AE = adverse event; BKZ = bimekizumab; NR = not reported; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SAE = serious adverse event.

^aAEs reported by ≥ 5% of patients in the BKZ 320 mg q.2.w. or q.4.w. treatment group.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Critical Appraisal

Internal Validity

Two RCTs included in the systematic review were conducted using similar study and statistical methods. No major concerns were identified in the methods used for randomization, allocation concealment, and treatment masking. In the BE HEARD I trial, there was a slight imbalance by sex, with a higher proportion of female patients than of male patients. In addition, duration of disease was slightly longer in the placebo group than in the treatment group. Despite these differences, the baseline patient characteristics were generally considered to be well balanced between the groups within the trials and were not considered to be a source of selection bias impacting efficacy findings.

The proportion of patients who discontinued study treatment was similar across the groups in the initial treatment period, and low overall, as less than 10% of patients in any treatment group discontinued study treatment. Across all groups, the proportion of discontinuations in the maintenance treatment phase was higher than the proportion of discontinuations in the initial treatment period, with a notably increased proportion of discontinuations in the placebo or bimekizumab 320 mg every 2 weeks group (32.3%). However, the rates of study discontinuations in both treatment periods in the BE HEARD I and II trials were not considered to have a substantial impact on overall study findings.

Although patients and investigators were blinded to study treatments, the observed imbalance in reported AEs for patients receiving bimekizumab, notably oral candidiasis, may have increased the likelihood that patients and investigators were aware of treatment assignments. There is also a potential risk of assessment bias for the evaluation of subjective outcomes such as HiSCR and flares, which are physician assessed and prone to interobserver variation in the assessment of lesion counts. In a previous study with patients with HS, HiSCR50 showed weak to moderate correlation in validity with other physician-rated assessments, despite showing a strong correlation with AN count (intraclass correlation coefficient = 0.91).³⁸ Similarly, it is possible that response bias could have influenced patient-reported outcomes such as skin pain response and HRQoL (assessed using the DLQI), as these require subjective reporting by patients.

The statistical methods for the analyses of the primary and secondary outcomes at week 16 in both trials were considered appropriate. Sample size calculations and power were adequate, and the primary and secondary outcome analysis considered the stratification factors at randomization, ensuring that prognostic balance between the groups were maintained. The exception was HSSDD worst pain responder rate, a ranked secondary end point, which was conducted in the subgroup of patients with baseline HSSDD worst pain greater than or equal to 3. Randomization was not stratified by baseline HSSDD. In both studies, study protocols were amended and reported before and after patients had been fully randomized to treatment groups (5 times for the BE HEARD I trial and 4 times for the BE HEARD II trial). One significant amendment, made after all participants had been randomized into both studies, included the addition of a new efficacy outcome (HSSDD worst skin pain item response). This amendment was considered to have minimal impact on the overall analysis, because the original sample size was based on change from baseline in worst skin pain for the comparison of bimekizumab 320 mg every 4 weeks versus placebo and was higher than the recalculated sample size. There were no amendments to study eligibility, which might have biased the study population included in the primary efficacy assessment. There were also many protocol deviations reported in both trials, most commonly, prohibited concomitant medication use. However, it was concluded that the protocol deviations had minimal impact on the primary efficacy outcome.

Appropriate data imputation methods and sensitivity analyses were conducted using different methods for handling missing data, including MI-MCMC monotone regression, last observation carried forward, composite estimand, nonresponse imputation, and tipping-point analyses. Findings from the primary analysis were consistent with the sensitivity analysis in both studies (except for the tipping-point analysis in the worst-case scenarios), and the impact of missing data on the primary and key secondary end points was minimal. Methods for control of type I error were used in both studies at week 16 and were considered appropriate. In the BE HEARD I trial, the primary and key secondary end points were ranked (HiSCR50, HiSCR75, DLQI,

HS skin pain change from baseline, and HS skin pain response), and statistical testing was performed using parallel gatekeeping frameworks to control the overall type I error rate at 0.05. The BE HEARD II trial employed a similar framework at the same significance levels, but also included flare by week 16 as a key secondary end point.

The primary and key secondary end points in both trials were assessed at week 16, which was considered appropriate relative to other clinical trials for HS. After week 16, there was limited evidence on the comparative efficacy of bimekizumab versus placebo for key efficacy outcomes (HiSCR50, flares, HSSDD responder rates, and DLQI) identified by the patient and clinician groups and the clinical experts consulted for this review. The BE HEARD trials included assessments from week 16 to week 48, during which all patients were switched to bimekizumab 320 mg every 2 weeks or every 4 weeks. While these data indicate whether a sustained treatment response was observed, the lack of a control group during the maintenance treatment period limits the ability to adequately assess comparative efficacy beyond 16 weeks.

Patient groups contributing to the review highlighted the need for treatments that improve HRQoL. The DLQI and HSSDD questionnaires were identified as important assessments of patient-reported outcomes by the clinical experts consulted for this review. The DLQI instrument is nonspecific to HS, assessing general changes in HRQoL for patients with dermatological conditions, and it has a moderate to strong correlation with other HRQoL tools.⁴⁶ The HSSDD is an HS-specific questionnaire used to assess skin pain based on a clinically meaningful improvement; the HSSDD has not been used in previous studies, but was reported to demonstrate validity, reliability, and responsiveness using data from the BE HEARD trials.⁴⁸ However, the missing data from these questionnaires at week 16 of both studies were identified as a concern limiting the interpretability of this outcome.

The use of concomitant medications in the safety set during the initial treatment period of both studies was similar across groups, ranging from 83.3% to 87.8% in the BE HEARD I trial and 78.4% to 79.3% in the BE HEARD II trial. There were no concerns regarding the impact of concomitant medication use in the trials on the primary outcome. The use of rescue medications was also considered appropriate and reflective of use in clinical practice. Rescue medication use, particularly analgesics and systemic antibiotics, was similar across the treatment groups in both trials; these uses were considered intercurrent events and imputed in the analysis using appropriate methods for handling missing data, and therefore these were not seen to impact the primary and key secondary outcomes.

External Validity

The patient populations included in the trials were generally in line with patients seen in clinical practice in Canada with respect to age, sex, Hurley stage, duration of disease, and prior antibiotic use. The experts noted that in their experience, the duration of HS and time to diagnosis were consistent with the experiences of patients in current practice. There were no major concerns regarding the generalizability of the baseline and demographic characteristics of the patients enrolled in the trials. Both trials were multinational studies with sites in Canada and many enrolled patients from Canada.

While the choice of placebo as a comparator in both studies was sufficient for assessing the efficacy and safety of bimekizumab in patients with HS, the use of an active comparator such as secukinumab

or adalimumab would have been ideal. The timing of the clinical trials may have made comparisons to secukinumab challenging; however, adalimumab would have been an ideal active comparator to evaluate relative safety and efficacy. The concomitant medications and procedures allowed during the trials aligned with those in clinical practice. There were no concerns with the rescue medications administered during the trials, as they aligned with drugs available in current practice.

The bimekizumab dosing and treatment schedule used in both trials aligns with the recommended dosing approved by Health Canada, which is bimekizumab 320 mg every 2 weeks for the first 16 weeks of treatment, followed by bimekizumab 320 mg every 4 weeks thereafter. While both studies included a group that received bimekizumab 320 mg every 4 weeks for the initial treatment period (first 16 weeks), efficacy and safety results from this group were not summarized for the purposes of this review, as the dosing schedule was outside of the approved indication. Although the 16-week duration of the initial treatment period was adequate to assess the clinical benefit of bimekizumab versus placebo in a clinical trial setting, the consulted clinical experts noted that a 6-month assessment is more applicable to clinical practice, as HS is often slow to respond to treatment. The experts noted that if after 16 weeks of treatment there is no response to treatment or there is disease worsening, they would consider discontinuing treatment. During the maintenance treatment period, patients received bimekizumab either every 2 weeks or every 4 weeks from week 16 to week 48. According to the consulted clinical experts, both dosage schedules (every 2 weeks and every 4 weeks) are applicable to clinical practice, as different dosage frequencies will likely be required, depending on disease stability. However, it is worth noting that the Health Canada–approved dosing recommendations for bimekizumab follow a fixed schedule and adjusting dosage frequency based on treatment response is not suggested.

The 48-week duration of treatment limits the generalizability of findings from both trials, as sufficient long-term evidence of safety and efficacy of bimekizumab treatment is not provided. Given that HS is a chronic, lifelong condition with no cure, there is a need for comprehensive long-term evaluation. Extended follow-up with an appropriate active comparator is necessary to understand the long-term efficacy and safety of bimekizumab in patients with moderate to severe HS.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the 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 for informing expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.^{14,15}

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate — The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. We use the word “likely” for evidence of moderate certainty (e.g., “X intervention likely results in Y outcome”).

- **Low certainty:** Our confidence in the effect estimate is limited — The true effect may be substantially different from the estimate of the effect. We use the word “may” for evidence of low certainty (e.g., “X intervention may result in Y outcome”).
- **Very low certainty:** We have very little confidence in the effect estimate — The true effect is likely to be substantially different from the estimate of effect. We describe evidence of very low certainty as “very uncertain.”

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.

For single arms of trials (not presented in [Table 2](#)): Although GRADE guidance is not available for noncomparative studies, the CDA-AMC review team assessed the noncomparative (48-week) outcomes for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials started at very low, certainty with no opportunity for rating up.

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 reference points for the certainty-of-evidence assessment for HiSCR50 response, flares, HSSDD worst skin pain based on a clinically meaningful response, and DLQI total score were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review. The reference point for the certainty-of-evidence assessment for DLQI total score was set according to the presence or absence of an important effect based on the threshold identified in the literature. The reference points for the certainty-of-evidence assessment for notable harms (candida infections) were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review.

For the GRADE assessments, findings from the BE HEARD studies at week 48 were considered together and summarized narratively per outcome because these studies were similar in population, interventions, design, and outcome measures.

Results of GRADE Assessments

Bimekizumab Versus Placebo

[Table 2](#) presents the GRADE summary of findings for bimekizumab every 2 weeks versus placebo.

Long-Term Extension Studies

Contents within this section have been informed by materials submitted by the sponsor. The following has been summarized and validated by the review team.

Description of Studies

Patients who had completed the maintenance treatment period of the BE HEARD I and II trials were eligible to enrol in a separate open-label, noncontrolled, extension trial, the BE HEARD EXT (NCT04901195) trial. The objective of the extension trial is to evaluate 2 bimekizumab dosing regimens (320 mg every 2 weeks and 320 mg every 4 weeks). This study was ongoing at the time of submission and was not submitted for this review.

Indirect Evidence

Contents within this section have been informed by materials submitted by the sponsor. The following has been summarized and validated by the review team.

Objectives for the Summary of Indirect Evidence

Direct comparative evidence for bimekizumab was limited to 2 placebo-controlled trials; however, relevant comparators for this review included secukinumab and adalimumab. To address this gap in the evidence, the sponsor submitted indirect evidence in the form of an NMA and an MAIC. The objective of this section is to summarize and critically appraise the methods and findings of the indirect evidence submitted by the sponsor.

Description of Indirect Comparisons

For outcomes reported from week 12 to week 16, NMAs were conducted by the sponsor and for outcomes reported from week 48 to week 52, unanchored MAIC methods were used.

The objective of the systematic literature review (SLR) was to identify RCT evidence on the efficacy and safety of bimekizumab and relevant comparators for the treatment of adult patients with HS. The SLR was conducted in April 2023 and included updated searches to October 2023. Adult patients (aged ≥ 18 years) with moderate to severe HS were the focus of the SLR, and systemic biologic therapy with dosing and administration as per marketing authorization or recommendations for HS treatment guided the inclusion of relevant comparators. Outcomes assessing disease severity or symptoms between weeks 12 and 16, or separately between weeks 48 and 52 of follow-up, were of primary interest. Data reported for outcomes during the week 12-to-16 time frame provided information on treatment comparisons before treatment crossover or rerandomization within the trials and were considered separately from data reported for outcomes during the week 48 to week 52 follow-up.

The clinical SLR was designed to capture English language publications (either full-text manuscripts or conference abstracts or posters) on RCTs performed in any country, and involving patients with HS. The electronic databases searched were Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials. These database searches were supplemented by handsearching of reference lists from conferences, health technology assessment submissions, clinical trial registries, and published SLRs and NMAs. Two

independent reviewers screened all publications against the predefined eligibility criteria at both the title plus abstract and full-text review stages. Data extraction and risk of bias assessment were performed by 1 reviewer and quality-checked by a second independent reviewer. Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool for RCTs, currently recommended by the National Institute for Health and Care Excellence (NICE).

The results of the October 2023 SLR update were used to inform the NMAs. To be included in the NMA, studies had to report outcome measurements after a minimum of 12 weeks of follow-up, but before crossover or rerandomization. Based on the available data, the time frame for the NMA was week 12 to week 16. Preference was given to the week 16 data if studies reported measurements at more than 1 time point within this time frame, as this aligned with the follow-up period for the primary and secondary end points in the BE HEARD I and II trials, the phase III trials for bimekizumab.

For short-term outcomes assessed between weeks 12 and 16, NMA methodology was used following the NICE Decision Support Unit recommendations for clinical data synthesis, and the analyses were conducted in WinBUGS. Where sufficient data were available, both fixed- and random-effects models were conducted with and without placebo adjustment.

It was not possible to conduct NMAs for long-term outcomes assessed at weeks 48 to 52 due to changes in the treatment schedule that occurred when the double-blind period of the trials was completed; as such, a connected treatment network through a common comparator was not possible and unanchored MAICs were conducted for this time point, following the established methods recommended in the NICE guidelines.

Fifteen outcomes of interest were included in the NMA and MAIC analyses ([Table 23](#)).

The majority of new data and outcomes of interest identified in the October 2023 SLR update were reported in the week 12-to-16 time frame, and thus the focus of the updates was to conduct an NMA bringing together all treatment data into a single network. The MAIC analyses were conducted using the trials and data identified from the original April 2023 SLR.

The SLR and updates (including the most recent October 2023 update) identified 34 relevant publications, reporting on 11 RCTs. Of these 11 RCTs, 9 trials (with 3,129 participants) reported outcome data of interest for relevant doses of bimekizumab (the HS0001, BE HEARD I, and BE HEARD II trials, with a total of 1,104 participants), secukinumab (the SUNSHINE and SUNRISE trials, with a total of 1,084 participants), and adalimumab (the NCT00918255, PIONEER I, PIONEER II, and SHARPS trials, with a total of 941 participants), and were included in the NMA.

Table 23: Outcomes of Interest for the Indirect Treatment Comparisons

Binomial outcomes	Continuous outcomes
Outcomes assessed at weeks 12 to 16	
Measured as number of patients achieving clinical benchmark at weeks 12 to 16 • HiSCR^a	Measured as change from baseline at weeks 12 to 16 for the following clinical scores • Change from baseline in IHS4

Binomial outcomes	Continuous outcomes
○ ≥ 50% improvement in HiSCR (HiSCR50) ○ ≥ 75% improvement in HiSCR (HiSCR75) ○ ≥ 90% improvement in HiSCR (HiSCR90) ○ ≥ 100% improvement in HiSCR (HiSCR100) ● Proportion of patients with ≥ 55% reduction in IHS4 score ● Proportion of patients experiencing flares: ○ ≥ 25% increase in AN count with an absolute increase in AN count of ≥ 2 relative to baseline ● Proportion of patients experiencing an MCID in DLQI: ○ Proportion of patients with ≥ 5-point reduction in DLQI from baseline^b ● Proportion of patients experiencing a serious adverse event ● Proportion of patients discontinuing study treatment due to any cause ● Proportion of patients discontinuing study treatment due to adverse events	● Change from baseline in absolute or % AN count ● Change from baseline in absolute or % DT count ● Change from baseline in absolute or % DLQI ● Change from baseline in worst skin pain score (NRS30)
Outcomes assessed at weeks 48 to 52	
Measured as number of patients achieving clinical benchmark at weeks 48 to 52 HiSCR ● ≥ 50% improvement in HiSCR (HiSCR50) ● ≥ 75% improvement in HiSCR (HiSCR75) ● ≥ 90% improvement in HiSCR (HiSCR90) ● Proportion of patients with a ≥ 50% improvement in AN count ● Proportion of patients experiencing an MCID in DLQI ● Proportion of patients with ≥ 5-point reduction in DLQI from baseline^b	Measured as change from baseline at weeks 48 to 52 for the following clinical scores ● Change from baseline in % AN count ● Change from baseline in % DT count

AN = abscess and inflammatory nodule; DLQI = Dermatology Life Quality Index; DT = draining tunnel; HiSCR = Hidradenitis Suppurativa Clinical Response; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HiSCR90 = Hidradenitis Suppurativa Clinical Response 90; HiSCR100 = Hidradenitis Suppurativa Clinical Response 100; IHS4 = International Hidradenitis Suppurativa Severity Score System; MCID = minimal clinically important difference; NMA = network meta-analysis; NRS = numerical rating scale.

^aHiSCR will also be analyzed as an ordered categorical model.

^bDLQI MCID definition differs across trials: for the BE HEARD I and II trials, it is ≥ 4-point reduction; in the SUNRISE and SUNSHINE trials, it is ≥ 5-point reduction. The NMA analyses used the BE HEARD trial data matched to ≥ 5-point reduction.

Source: Indirect Treatment Comparison Report.⁵⁰

Indirect Treatment Comparison Design

Objectives

As per the sponsor's submission, the objective was to conduct an NMA comparing bimekizumab to secukinumab and adalimumab.

Study Selection Methods

The SLR had 2 objectives:

Analysis scope: Identify recent RCT evidence on the efficacy and safety of bimekizumab, adalimumab, and secukinumab for the treatment of adult patients with HS, to update an SLR previously conducted in April 2023.

Expanded scope: Identify RCT evidence on the efficacy and safety of biologic therapies (IL-17A inhibitors, IL-17A/F inhibitors, and TNF-alpha inhibitors) and synthetic therapies (i.e., Janus kinase inhibitors) for the treatment of adult patients with HS, by conducting a de novo search without date limits. A de novo clinical SLR was conducted to identify RCTs on the effect on HS of biologic and synthetic therapies other than those indicated in the analysis scope. The rationale for this was not for the studies to be included in the NMA, but to identify studies that assessed off-label therapy or therapies in development, thereby providing certainty that all relevant therapies were captured in the NMA. No data were extracted from the publications identified.

NMA Methods

To be included in the NMA, studies had to report outcome measurements after a minimum of 12 weeks of follow-up, but before crossover or rerandomization. Based on the available data, the time frame used for this NMA was 12 to 16 weeks. Preference was given to the week-16 data if studies reported measurements at more than 1 time point within this time frame, as this aligned with the time points for the primary and secondary end points in the BE HEARD I and II trials.

A global evidence network was generated that included all the studies identified for inclusion in the NMAs. Individual treatment comparator specific networks were only used for studies that did not report data for an outcome of interest for either adalimumab or secukinumab, or the data analysis methodologies used were not considered comparable. Two evidence networks by prior treatment were generated:

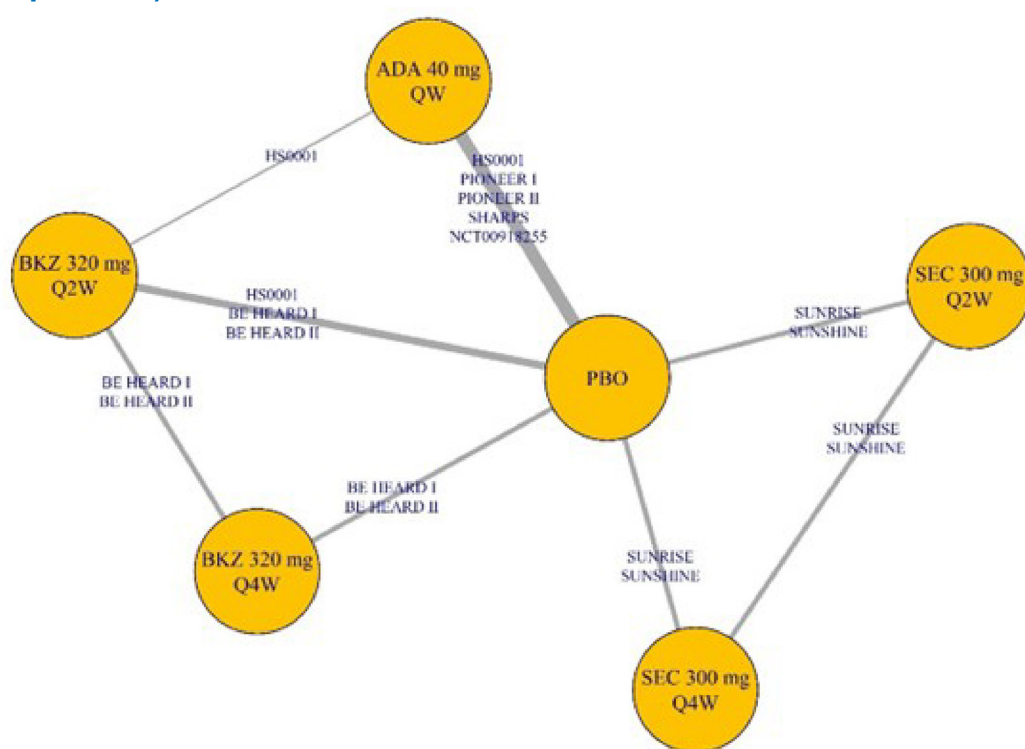
- Global network population with mixed biologic-experienced and biologic-naïve populations, which includes all studies and patients with relevant outcome data, regardless of previous biologic therapy exposure status ([Figure 4](#)):
 - Few patients were biologic experienced across the studies, with some studies enrolling only patients who were biologic naïve. For studies that included a proportion of patients with prior biologic therapy experience, data from biologic-naïve subgroups were only available for a small number of outcomes. Therefore, to provide as comprehensive an analysis as possible, all study participants were included in a global network and provide a proxy for a biologic-naïve group.
 - A global comparison of patients who were exclusively biologic naïve was not conducted because a very small number of outcomes were consistently available for all treatments in this subgroup.
- Biologic-experienced subgroup with patients who had previously received systemic biologic treatment, including IL-17 inhibitors and/or TNF-alpha inhibitors:
 - Consistently reported definition across trials identified as prior biologic treatment for HS.
 - As for the pure biologic-naïve subgroup, there are few outcomes for this subgroup across the network including all treatments. However, exploring the patient outcomes that are available will offer additional evidence for the relative efficacy of bimekizumab versus comparators.

[Figure 4](#) presents the global network of evidence for the NMAs for the mixed biologic-experienced and biologic-naïve population. The network includes each of the 9 studies identified for the analyses: the PIONEER I, PIONEER II, NCT00918255, and HS0001 studies enrolled only patients who did not have experience with biologics; the BE HEARD I and II studies and the SUNRISE and SUNSHINE studies enrolled a small proportion of patients who had experience with biologics; and the SHARPS study did not state patients' prior biologic therapy status.

[Figure 5](#) presents the network of evidence for the NMAs in the biologic-experienced patient subgroup. The network includes 4 studies and includes doses of bimekizumab, secukinumab, and placebo only. No study enrolled exclusively patients with biologic experience, with each subgroup representing between 13% and 25% of the original sample sizes in the trials (refer to [Table 41](#) in [Appendix 1](#) for the proportion of patients with prior systemic biologic therapy experience per study).

Evidence Networks

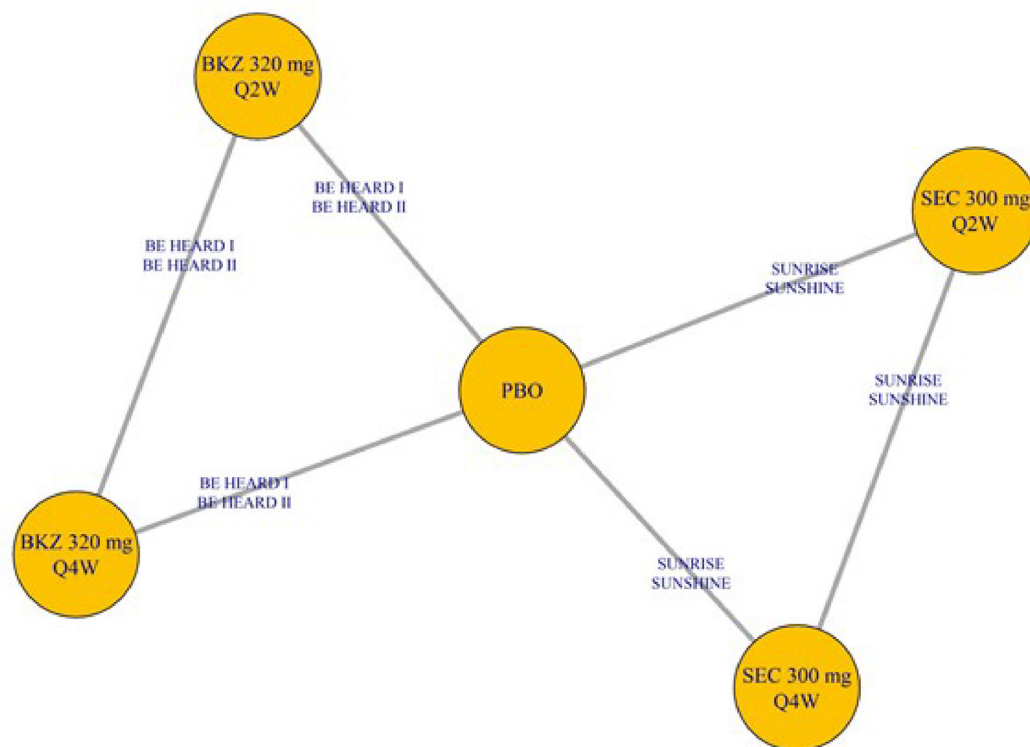
Figure 4: Global Network of Evidence (Mixed Biologic-Experienced and Biologic-Naïve Population)



ADA = adalimumab; BKZ = bimekizumab; PBO = placebo; QW = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; SEC = secukinumab.

Source: Indirect Treatment Comparison Report.⁵⁰

Figure 5: Global Network of Evidence (Biologic-Experienced Population)



BKZ = bimekizumab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SEC = secukinumab.

Source: Indirect Treatment Comparison Report.⁵⁰

Matching-Adjusted Indirect Comparison

The sponsor's Summary of Clinical Evidence indicated that MAICs were required at the pooled later time point (weeks 48 to 52) because crossover was permitted in the trials after the week 12-to-16 time point and the longer-term data (from weeks 48 to 52) were not placebo controlled. As such, a connected network could not be formed. Independent networks were formed for each MAIC. Analyses were only performed in the overall trial populations because subgroup data for patients who were biologic naive or biologic experienced were not available at weeks 48 to 52 for adalimumab or secukinumab.

For all comparator interventions used in this analysis, the sponsor focused on dosing that was consistent with the marketing authorization for HS and for bimekizumab in other countries, which is consistent with the recommended dosing approved by Health Canada.

[Table 24](#) summarizes the treatment arms included in the base-case MAIC analysis.

Table 24: Summary of Study Arms Included in the MAIC

Group for MAIC	Study arm	Studies with this arm
BKZ q.2.w. or q.4.w.	BKZ 320 mg q.2.w. at week 0 to 16, then BKZ 320 mg q.4.w. at week 17 to 48	Pooled BE HEARD trials
ADA q.w.	ADA 40 mg q.w.	PIONEER OLE
SEC q.4.w. SEC q.2.w.	SEC 300 mg q.4.w. SEC 300 mg q.2.w.	Pooled SUNRISE and SUNSHINE

ADA = adalimumab; BKZ = bimekizumab; OLE = open-label extension; MAIC = matching-adjusted indirect comparison; q.w. = every week; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SEC = secukinumab.

Source: Indirect Treatment Comparison Report.⁵⁰

Indirect Treatment Comparison Analysis Methods

Network Meta-Analyses

[Table 25](#) describes the analysis methods used in the NMA.

Table 25: NMA Analysis Methods^{51,52}

Methods	Description
Analysis methods	Bayesian NMA was conducted using standard methods for clinical data synthesis. The analysis was conducted in WinBUGS using validated model code available from the NICE Decision Support Unit. Where sufficient study data were available, meta-regression models to adjust for baseline risk (placebo-adjusted models) and models without placebo adjustment were both conducted, to explore any differences in placebo effect across trials that may introduce bias into the relative treatment effect. Placebo-adjusted models are useful when there is evidence to suggest that placebo effect sizes have increased over time. Bubble plots were used to explore the increase in placebo effect size across the trials. A global network comprising all studies was developed for the base case. Because the sponsor considered that secukinumab is likely the key comparator for bimekizumab, the primary imputation method for the secukinumab studies was applied by the sponsor to the bimekizumab studies in the base case to ensure intercurrent events were accounted for in the data analysis. This comprised modified nonresponder imputation and accounting for HS-related antibiotic use. The primary output from WinBUGS is the relative treatment effect compared with the reference treatment, which is placebo in the case of this analysis. From these outputs, other estimates can be calculated, such as the relative treatment effects comparing all treatments in the network. The relative treatment estimates from the logit model are the (log) odds ratio (OR), and from the probit model are z-scores. The relative treatment effect estimates from the continuous models are mean differences in the change from baseline.
Priors	Uninformative priors were used for the between-study standard deviation, assuming that the heterogeneity is the same across all comparisons.
Assessment of model fit	The trial arm data were fitted to a generalized linear model via Bayesian Markov Chain Monte Carlo methods. The WinBUGS model was run for a minimum burn-in of 20,000 iterations to maximize convergence. Subsequently, 3 chains of 10,000 samples were drawn from the posterior distributions. The mean residual deviance (total residual deviance divided by number of data points) and the DIC output from WinBUGS provide an overall estimate of how well the predicted values fit the observed dataset. The DIC was used to compare different models for the same likelihood and data. An alternative form of the DIC was also estimated (alt DIC = total residual

Methods	Description
	deviance + posterior variance). The model with the lowest DIC/alt DIC was deemed to best predict a replicate dataset of the same structure to that observed. Differences in DIC of > 10 should rule out the model with the highest DIC, whereas if the difference is < 5, then other criteria, such as average residual deviance and CrI range, are used to judge model fit. In addition, to assess whether the meta-regression (placebo-adjusted) model was better for analysis than the unadjusted model, the regression coefficient and associated 95% CrI were examined to determine whether the 95% CrI excludes 0 and whether the between-study standard deviation parameter and 95% CrI are reduced in magnitude. In the cases where the placebo-adjusted model was not appropriate or did not converge for specific outcomes, the results from the unadjusted model provide the base case. Both fixed-effects and random-effects models were tested. Fixed-effects models assume that all studies estimate the same underlying effect, and random-effects NMAs allow the true treatment effect (e.g., OR between 2 treatments) to vary between studies due to heterogeneity. For the HiSCR efficacy outcomes (HiSCR50, HiSCR75, HiSCR90, and HiSCR100), for consistency across the 4 outcomes and based on the model fit, the sponsor concluded that the fixed-effects placebo-adjusted model was preferred. The sponsor claimed that the fixed-effects non-placebo-adjusted model provided a better fit and the most robust results for other efficacy outcomes with fewer included data points.
Assessment of consistency	The sponsor stated that it was not possible to assess consistency between the direct and indirect analysis estimates in the network as the loops in the network were all informed by three-arm trials, which by design cannot be inconsistent.
Assessment of convergence	The sponsor did not describe how they assessed convergence.
Outcomes	• HiSCR50, HiSCR75, HiSCR90, and HiSCR100 • Proportion of patients with $\geq 55\%$ reduction in IHS4 score • Proportion of patients experiencing flares • Proportion of patients experiencing an MCID in DLQI • Proportion of patients experiencing a serious adverse event • Proportion of patients discontinuing treatment due to any cause • Proportion of patients discontinuing treatment due to adverse events
Follow-up time points	The NMA assessed outcomes at weeks 12 to 16
Construction of nodes	Networks were created using the common comparator, placebo, at the connecting node.
Sensitivity analyses	The HiSCR50, HiSCR75, and HiSCR90 responses are dependent on each other and not mutually exclusive, for example, patients who experience an HiSCR75 response are a subset of those experiencing an HiSCR50 response. Therefore, an alternative model using a multinomial analysis with probit link was used to incorporate all the evidence from each of the HiSCR response categories.

CrI = credible interval; DIC = deviance information criterion; DLQI = Dermatology Life Quality Index; HiSCR = Hidradenitis Suppurativa Clinical Response; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HiSCR90 = Hidradenitis Suppurativa Clinical Response 90; HiSCR100 = Hidradenitis Suppurativa Clinical Response 100; HS = hidradenitis suppurativa; IHS4 = International Hidradenitis Suppurativa Severity Score System; MCID = minimal clinically important difference; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; OR = odds ratio.

Source: Indirect Treatment Comparison Report.⁵⁰

Definition of Intercurrent Event Across Studies

Accounting for the effect of intercurrent events for patients receiving antibiotics was considered a key element when assessing primary outcomes in both the BE HEARD I and II trials (bimekizumab) and the

SUNRISE and SUNSHINE (secukinumab) trials, and analyses adjusted to account for these events are presented in the primary publications. However, the definitions of the modified nonresponder imputation estimand varied across these trials and were also different from the primary estimands reported for the older PIONEER and SHARPS (adalimumab) trials and the HS0001 (bimekizumab) trial, none of which accounted for intercurrent events (except for efficacy analyses from the PIONEER I trial, for which patients receiving rescue medication were counted as nonresponders for categorical variables after the start of rescue medication; study discontinuation was not adjusted for).

An intercurrent event in the BE HEARD trials was defined as receipt of systemic antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy. Receipt of systemic antibiotic rescue medication was defined as initiating any systemic antibiotic on or after baseline for any reason (including in response to an AE). For the primary analysis, a patient was considered a nonresponder if they experienced an intercurrent event and missing data were imputed, that is, they received antibiotics for any reason or discontinued study treatment due to an AE or lack of efficacy. Intercurrent events were incorporated into the primary analysis of the primary and ranked secondary end points: HiSCR50 response, HiSCR75 response, change from baseline in DLQI total score, change from baseline in HSSDD worst skin pain score, and worst skin pain response.

In the SUNRISE and SUNSHINE trials, an intercurrent event was defined as receipt of rescue antibiotic therapy, as was permanent discontinuation of study treatment due to AEs or lack of efficacy. Rescue antibiotic therapy was defined as antibiotics for the treatment of HS if a patient experienced an increase in AN count of at least 3. For the primary analysis, a patient was considered to be a nonresponder if they experienced an intercurrent event, that is, they received antibiotics for HS or permanently discontinued study treatment due to AEs or lack of efficacy, and missing data were imputed.

Bimekizumab data from the HS0001, BE HEARD I, and BE HEARD II trials were reanalyzed to match more closely the intercurrent event–handling strategies used in the comparator trials. A summary of the definition for the key terms used for the different end points is presented in [Table 26](#).

Table 26: Estimands and Imputation or Missing Data Strategies Reported Across Included Trials

Estimand or imputation method	Description
Key estimands	
ALL-ABX	Primary estimand for the BE HEARD trials. Any antibiotic use was considered an intercurrent event in the estimand, in addition to permanent discontinuation of study treatment due to AEs or lack of efficacy ^a
HS-ABX	Primary estimand for the SUNRISE and SUNSHINE trials. Antibiotic rescue therapy for HS was considered an intercurrent event in the estimand, in addition to permanent discontinuation of study treatment due to AEs or lack of efficacy. ^a
Observed case	All patients who had an observation at the end-point visit, nonimputation for intercurrent events or missing data

Estimand or imputation method	Description
Key imputation and missing data–handling strategies	
LOCF	Missing data are imputed by carrying the last observation forward
MI	Multiple imputation generates values for missing data from distributions of and relationships among observed variables in the dataset
MMRM	Data collected from all patients (including those who drop out) are used to predict mean longitudinal outcomes
mNRI	Patients who drop out or experience an intercurrent event, regardless of their actual response status at the time of dropping out or the intercurrent event, are assumed to be nonresponders (refer to the descriptions of <i>ALL-ABX</i> and <i>HS-ABX</i> [in Table 26] for the alternative definitions of intercurrent events), and missing data are imputed
NRI	Missing data are imputed using NRI. Patients who have missing data at the time point of interest are assumed to have disease that has not responded to treatment. ^b

ALL-ABX = any antibiotic use; AE = adverse event; HS = hidradenitis suppurativa; HS-ABX = hidradenitis suppurativa–specific antibiotic use; LOCF = last observation carried forward; MI = multiple imputation; MMRM = mixed model repeated measures; mNRI = modified nonresponder imputation; NRI = nonresponder imputation.

^aIf an intercurrent event occurred, the patient was considered to have missing data following the event and outcomes were imputed in the same way as for other missing data.

^bExcept for efficacy analyses from the PIONEER I trial, for which patients receiving rescue medication were also counted as nonresponders for categorical variables after the start of rescue medication.

Matching-Adjusted Indirect Comparison

MAIC is a nonparametric likelihood reweighting method for comparing treatment effects while minimizing bias that results from prognostic or effect-modifying baseline characteristics that are imbalanced across trial populations. This is achieved by utilizing individual patient-level data from a trial to generate weights for each patient, based on the overrepresentation or underrepresentation of the average characteristics in a comparator trial population. These weights are then incorporated into a regression analysis to generate results weighted to the comparator trial population.

Because patients in the placebo arm of the BE HEARD trials switched to bimekizumab at week 16, it was not possible to form a connected network at week 48. Therefore, an unanchored population-adjusted method was required to compare long-term outcomes. While an anchored MAIC is preferable to preserve randomization within the studies, it was not feasible in this analysis as there was no common comparator at week 48 because of the design of the included trials. Therefore, an unanchored approach was undertaken in which individual patient-level data from the bimekizumab trials were matched to aggregated baseline characteristics of the comparator trials. All MAIC analyses were conducted using R software.

To adjust for cross-trial differences, patients from the bimekizumab trials were reweighted to match the baseline characteristics of the relevant comparator trial patients; treatment-effect modifiers were identified, with input from the sponsor's clinical advisors, from the variables presented in [Table 27](#). Variables were always considered, where available, with the exception of:

- individual components of AN count (that is, abscesses and inflammatory nodules, as there is collinearity between these variables and the combined AN count)

- DLQI, a patient-reported outcome, which when included as a matching variable resulted in a disproportionate reduction in the effective sample size, in addition to it not being standard practice to include patient-reported outcomes as covariates in MAIC analyses.

Table 27: Included and Excluded Matching Variables for Adjustment of Baseline Patient Population (MAIC Analysis)

Variables	PIONEER I	PIONEER II	PIONEER OLE (Scenario)	SUNSHINE	SUNRISE
Males (%) ^a	Yes	Yes	Yes	Yes	Yes
Age (years) ^a	Yes	Yes	N-only median	Yes	Yes
White (%) ^a	Yes	Yes	Yes	Yes	Yes
Smoking (%) ^a	Yes	Yes	Yes	Yes	Yes
BMI ^a	Yes	Yes	NR	Yes	Yes
US region (%) ^a	Yes	Yes	NR	Yes	Yes
Hs-CRP ^a	Yes	Yes	N-only median	NR	NR
Prior biologics (%) ^a	Yes	Yes	NR	Yes	Yes
Concomitant antibiotics (%) ^a	NR	NR	NR	Yes	Yes
Hurley stage III (%) ^a	Yes	Yes	Yes	Yes	Yes
AN count ^a	Yes	Yes	N-only median	Yes	Yes
Abscess count	No	No	N-only median	No	No
DT count ^a	Yes	Yes	N-only median	Yes	Yes
Inflammatory nodule count	No	No	NR	No	No
DLQI	No	No	NR	NR	NR
HS duration (years)	N-only median	N-only median	NR	Yes	Yes

AN = abscess and inflammatory nodule; BMI = body mass index; DLQI = Dermatology Life Quality Index; DT = draining tunnel; HS = hidradenitis suppurativa; hs-CRP = high-sensitivity C-reactive protein; MAIC = matching-adjusted indirect comparison; NR = not reported; OLE = open-label extension.

^aIncluded matching variable.

Source: Indirect Treatment Comparison Report.⁵⁰

For the adalimumab versus bimekizumab base-case MAICs, baseline characteristics for the original groups of patients enrolled in the core PIONEER I and II trials were used for the matching. This assumed that the distribution of baseline characteristics across these patients was reflective of the subgroup of patients entering the open-label extension study. To investigate the stability of the results based on this assumption, a scenario analysis for bimekizumab versus adalimumab was conducted using a more limited set of baseline characteristics for matching based on those who entered the PIONEER open-label extension study. The restricted list was a pragmatic decision as many variables of interest were only available as median aggregate values. This scenario analysis may be more representative of the patients in the week 48 analysis, although it is not conventional to use a restricted set of baseline characteristics in an unanchored comparison.

The base-case analyses for the MAICs used time points of 48 weeks (for the adalimumab comparison) and 52 weeks (for the secukinumab comparison).

Results

Summary of Included Studies

Of the 11 unique RCTs included in the SLR, 9 were included in the NMA. Details of the included studies are summarized in [Table 40](#) ([Appendix 1](#)). One was excluded because of an irrelevant comparator, and 1 used an unlicensed dosage. All 9 of the studies included in the NMA evidence base were placebo controlled; of these, 3 studies evaluated bimekizumab, 4 studies evaluated adalimumab, and 2 studies evaluated secukinumab. The HS0001 study compared patients who received bimekizumab with both patients who received adalimumab and those who received placebo, and the SHARPS study compared patients who received adalimumab and underwent surgery to those who received placebo and underwent surgery ([Table 40](#)).

All the trials were double-blind, multicentre, international RCTs. Most trials were phase III, except for the HS0001 (phase II), NCT00918255 (phase II), and SHARPS (phase IV) trials. The length of the initial double-blind period was 12 weeks in the HS0001, PIONEER I, PIONEER II, and SHARPS trials and 16 weeks in the BE HEARD I, BE HEARD II, NCT00918255, SUNRISE, and SUNSHINE trials. Four of the trials (the PIONEER I, PIONEER II, SUNRISE, and SUNSHINE trials) included rerandomization at the end of their initial double-blind period, although in all studies except the SHARPS trial, the treatment schedule changed in at least 1 arm after the end of the double-blind period. The total length of follow-up ranged from 24 weeks to 52 weeks ([Table 40](#), [Appendix 1](#)).

The baseline population characteristics are summarized in [Table 41](#) ([Appendix 1](#)). Mean age ranged from 35.5 years (the PIONEER II trial) to 37.6 years (the SHARPS trial). Mean body mass index (BMI) ranged from 31.8 (the SUNRISE trial) to 34.8 (the HS0001 trial); the mean BMI in each of these studies is in the obesity range. BMI was not reported for the NCT00918255 trial. Mean AN count ranged from 10.8 (the SHARPS trial) to 17.7 (the HS0001 trial). The 3 bimekizumab studies had the highest AN counts; each count was greater than 16. The AN count was not reported for the NCT00918255 trial. Mean number of abscesses ranged from 1.7 (the NCT00918255 trial) to 4.8 (the HS0001 trial). The mean draining tunnel count ranged from 2.6 (the SUNSHINE trial) to 4.5 (the NCT00918255 trial). Mean baseline DLQI score ranged from 10.8 (the BE HEARD II trial) to 16.1 (the PIONEER I trial). The 3 bimekizumab studies had a lower mean baseline DLQI (10.8 to 12.6) compared with the 2 PIONEER studies (14.5 to 16.1). The higher DLQI score, the more quality of life is impaired, suggesting a slightly lower impact on the patients' lives in the bimekizumab studies. Mean HS duration ranged from 7.0 years (the BE HEARD II trial) to 12.4 years (the NCT00918255 trial). The mean duration of HS in most of the studies was less than 10 years, the exception being the SHARPS (10.9 years) and NCT00918255 (12.4 years) trials. The proportion of male patients in the trials ranged from 29.4% (the NCT00918255 trial) to 49.3% (the BE HEARD II trial). The proportion of white patients ranged from 72.5% (the NCT00918255 trial) to 94% (the SHARPS trial). The proportion of Asian patients ranged from 1.3% (BE HEARD I) to 12.2% (the SUNRISE trial); the PIONEER I, PIONEER II, NCT00918255, and

SHARPS trials did not report the proportion of Asian patients. The proportion of patients recruited in the US varied from 15.2% (the SUNRISE and SUNSHINE trials) to 74.5% in (the NCT00918255 trial).

The proportion of current smokers ranged from 43.0% (the BE HEARD I trial) to 68% (the SHARPS trial); the HS0001 trial did not report the proportion of current smokers. The proportion of Hurley stage III patients ranged from 29.4% (the NCT00918255 trial) to 51% (the HS0001 trial). There were patients who were biologic treatment-naïve in each trial; the proportion of patients who had previous experience with biologics ranged from 0.0% (the HS0001, PIONEER I, PIONEER II, and NCT00918255 trials) to 25.1% (the BE HEARD I trial). The SHARPS trial did not report the proportion of patients who had previous experience with biologics.

NMA for Outcomes Assessed at Weeks 12 to 16

Mixed Biologic-Experienced and Biologic-Naïve Population

[Table 28](#) and [Table 29](#) summarize the results of the NMA for binary outcomes at weeks 12 to 16. The presented results are from the fixed-effects placebo-adjusted model for HiSCR data and from the fixed-effects non-placebo-adjusted model for the other outcomes. The results are also presented for the random-effects models.

The results of the HiSCR50 analysis favoured bimekizumab every 2 weeks over secukinumab every 2 weeks (OR = 1.70; 95% CrI, 1.16 to 2.45) and over secukinumab every 4 weeks (OR = 1.69; 95% CrI, 1.14 to 2.43), for the fixed-effects models. The results observed in the random-effects model had 95% CrIs that crossed the null for the comparison of bimekizumab every 2 weeks versus secukinumab every 2 weeks () and versus secukinumab every 4 weeks ().

The results of the HiSCR50 analysis had 95% CrIs that crossed the null for the comparison of bimekizumab every 2 weeks versus adalimumab every week for the fixed-effects model (OR = 1.30; 95% CrI, 0.85 to 1.92) and the random-effects model ().

The results of the HiSCR75 analysis also favoured bimekizumab every 2 weeks over secukinumab every 2 weeks (OR = 2.02; 95% CrI, 1.38 to 3.20) and over secukinumab every 4 weeks (OR = 1.85; 95% CrI, 1.26 to 2.90), for the fixed-effects models. The results of the HiSCR75 analysis favoured bimekizumab every 2 weeks over secukinumab every 2 weeks () and over secukinumab every 4 weeks (), for the random-effects models.

The results of the HiSCR75 analysis favoured bimekizumab every 2 weeks over adalimumab every week (OR = 1.60; 95% CrI, 1.10 to 2.60) for the fixed-effects model. In the random-effects model, the results of the HiSCR75 analysis for the comparison of bimekizumab every 2 weeks versus adalimumab every week did not favour either treatment, with 95% CrIs that crossed the null ().

The results for the random-effects models show greater imprecision and some of the results that favoured bimekizumab in the fixed-effects models do not show the same degree of benefit in the random-effects models (the CrI crossed the null). The sponsor did not provide adequate justification for preferring the fixed-

effects models, and therefore, the random-effects models need to be considered in the evaluation of the relative efficacy of bimekizumab.

For the continuous outcome of mean change from baseline in DLQI, the 95% CrI crossed the null for the comparison of bimekizumab every 2 weeks versus adalimumab every 2 weeks (■■■■■).

Predominantly Biologic-Experienced Subgroup

The results of the HiSCR50 analysis for the comparison of bimekizumab every 2 weeks versus secukinumab every 2 weeks did not favour either treatment, with 95% CrIs that crossed the null (OR = 1.97; 95% CrI, 0.67 to 6.27) (Table 30). The results of the HiSCR50 analysis for the comparison of bimekizumab every 2 weeks versus secukinumab every 4 weeks also did not favour either treatment, with 95% CrIs that crossed the null (OR = 1.90; 95% CrI, 0.65 to 6.00).

There was no comparative evidence available for bimekizumab versus adalimumab for the biologic-experienced subgroup.

Table 28: Summary of Global NMA Binary Efficacy Outcomes (HiSCR50, HiSCR75, HiSCR90, HiSCR100) — OR (95% CrI) (Mixed Biologic-Experienced and Biologic-Naive Population)

Comparison		HiSCR50 (mNRI HS-ABX)	HiSCR75 (mNRI HS-ABX)	HiSCR90 (mNRI HS-ABX)	HiSCR100 (mNRI HS-ABX)
Number of studies (number of patients), N		9 (3,114)	7 (2,821)	7 (2,821)	5 (2,188)
BKZ q.2.w. vs. comparator	Model	OR (95% CrI) ^a	OR (95% CrI) ^a	OR (95% CrI) ^a	OR (95% CrI) ^a
SEC q.2.w. ^b	Fixed effects	1.70	2.02	1.86	1.77
	Random effects	(1.16 to 2.45) ^c ■■■■■	(1.38 to 3.20) ^c ■■■■■	(1.30 to 2.75) ^c ■■■■■	(1.12 to 2.77) ^c ■■■■■
SEC q.4.w.	Fixed effects	1.69	1.85	1.62	1.88
	Random effects	(1.14 to 2.43) ^c ■■■■■	(1.26 to 2.90) ^c ■■■■■	(1.13 to 2.36) ^c ■■■■■	(1.18 to 3.00) ^c ■■■■■
ADA q.w.	Fixed effects	1.30	1.60	1.56	1.60
	Random effects	(0.85 to 1.92) ■■■■■	(1.10 to 2.60) ^c ■■■■■	(1.10 to 2.28) ^c ■■■■■	(0.42 to 8.22) ■■■■■

ADA = adalimumab; BKZ = bimekizumab; CrI = credible interval; HiSCR50 = Hidradenitis Suppurativa Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HiSCR90 = Hidradenitis Suppurativa Clinical Response 90; HiSCR100 = Hidradenitis Suppurativa Clinical Response 100; HS = hidradenitis suppurativa; HS-ABX = hidradenitis suppurativa-specific antibiotic use; mNRI = modified nonresponder imputation; NMA = network meta-analysis; OR = odds ratio; q.w. = every week; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SEC = secukinumab; vs. = versus.

^aOR = 1 is the line of no effect.

^bDosage (300 mg q.2.w.) recommended for patients with HS that has not responded to SEC q.4.w. after week 16 to 28.

^cSignificant difference in favour of BKZ.

Source: Indirect Treatment Comparison Report.⁵⁰

Table 29: Summary of Global NMA Binary Efficacy Outcomes for Bimekizumab Every 2 Weeks at Weeks 12 to 16 — OR (95% CrI) (Mixed Biologic-Experienced and Biologic-Naive Population)

Comparison		Patients with flares (NRI)	Reduction in worst skin pain (NRS30) (mNRI HS-ABX)	DLQI MCID 5-point reduction (OC)
Number of studies (number of patients), N				
BKZ q.2.w. vs. comparator	Model	OR (95% CrI)^a	OR (95% CrI)^a	OR (95% CrI)^a
SEC q.2.w. ^b	Fixed effects			
	Random effects			
SEC q.4.w.	Fixed effects			
	Random effects			
ADA q.w.	Fixed effects			
	Random effects			

ABX = antibiotics; ADA = adalimumab; BKZ = bimekizumab 320 mg; CrI = credible interval; DLQI = Dermatology Life Quality Index; HS = hidradenitis suppurativa; HS-ABX = hidradenitis suppurativa-specific antibiotic use; MCID = minimal clinically important difference; mNRI = modified nonresponder imputation; NMA = network meta-analysis; NR = not reported (not included in network); NRI = nonresponder imputation; NRS = numerical rating scale; OC = observed case; OR = odds ratio; q.w. = every week; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SEC = secukinumab; vs. = versus.

^aOR = 1 is the line of no effect.

^bDosage (300 mg q.2.w.) recommended for patients with HS that has not responded to SEC q.4.w. after week 16 to 28.

^cSignificant difference in favour of BKZ.

Source: Indirect Treatment Comparison Report.⁵⁰

Table 30: Summary of Bimekizumab Every 2 Weeks Network Efficacy Outcomes at Weeks 12 to 16 — OR (95% CrI) (Biologic-Experienced Population)

Comparison	HiSCR50 (mNRI HS-ABX)
BKZ q.2.w. vs. comparator	OR^b (95% CrI)
SEC q.2.w.	1.97 (0.67 to 6.27)
SEC q.4.w.	1.90 (0.65 to 6.00)
ADA q.w.	NR

ADA = adalimumab; BKZ = bimekizumab; CrI = credible interval; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HS-ABX = hidradenitis suppurativa-specific antibiotic use; mNRI = modified nonresponder imputation; OR = odds ratio; q.w. = every week; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SEC = secukinumab; vs. = versus.

^aPresented models are suggested base-case results, mostly based on model fit parameters and 95% CrI.

^bOR = 1 is the line of no effect.

Source: Indirect Treatment Comparison Report.⁵⁰

MAIC for Outcomes Assessed at Weeks 48 to 52

[Table 35](#) and [Table 36](#) summarize the results of the MAIC for outcomes at week 48 (secukinumab) and week 48 (adalimumab).

Bimekizumab Versus Secukinumab (at Weeks 48 to 52)

[Table 31](#) presents the pooled baseline characteristics in the BE HEARD I and II trials before and after matching to the SUNRISE and SUNSHINE trials. All available variables were adjusted for, and the matching process reasonably replicated the pooled average baseline characteristics of the SUNRISE and SUNSHINE trials. The effective sample size remained greater than or equal to 70% of the BE HEARD trials and the sample size reduction was similar across the outcomes ([Table 32](#)).

[Table 35](#) presents the MAIC results of bimekizumab versus secukinumab at weeks 48 to 52. The results favour bimekizumab over secukinumab every 2 weeks and over secukinumab every 4 weeks for HiSCR50, HiSCR75, HiSCR90, and DLQI MCID 5-point reduction. The 95% Crls do not cross the null for any of these comparisons.

Bimekizumab Versus Adalimumab (at Week 48)

[Table 33](#) presents the pooled baseline characteristics in the BE HEARD I and II trials before and after matching to the PIONEER trials. All available variables were adjusted for, and the matching process reasonably replicated the pooled average baseline characteristics of the PIONEER trials. The effective sample size remained greater than or equal to 45% of the BE HEARD trials and the sample size reduction was similar across the outcomes ([Table 31](#)).

[Table 36](#) presents the MAIC results of bimekizumab versus adalimumab at week 48. The results favour bimekizumab over adalimumab for HiSCR50 but not for HiSCR75 and HiSCR90. The 95% Crls do not cross the null for the HiSCR50 results, but do cross the null for the HiSCR75 and the HiSCR90 results.

Table 31: Pooled Baseline Characteristics in BE HEARD Before and After Matching to SUNRISE and SUNSHINE (Bimekizumab vs. Secukinumab Comparison)

Characteristics	SUNRISE + SUNSHINE (SEC)	BE HEARD I + BE HEARD II (BKZ q.2.w. or q.4.w.)	
		Before matching	After matching
q.2.w. (N = 361)			
Age, mean (SD)	37.20 (12.01)	36.98 (12.36)	37.20 (12.01)
BMI, mean (SD)	32.25 (7.85)	32.67 (7.85)	32.25 (7.85)
Duration of HS (years), mean (SD)	7.25 (7.52)	8.23 (7.62)	7.25 (7.52)
AN count, mean (SD)	13.40 (9.75)	17.12 (16.72)	13.40 (9.75)
DT count, mean (SD)	2.95 (3.50)	3.78 (4.43)	2.95 (3.50)
Male, %	162 (45.00)	118 (40.55)	102 (45.00)
White, %	278 (77.01)	232 (79.73)	174 (77.01)
Smoking, %	193 (53.50)	134 (46.05)	121 (53.50)
Hurley stage III, %	153 (42.49)	131 (45.02)	96 (42.49)
Prior biologics, %	79 (22.01)	56 (19.24)	50 (22.01)
Concomitant antibiotics, %	43 (12.01)	28 (9.62)	27 (12.01)
US region, %	55 (15.20)	87 (29.90)	34 (15.20)

Characteristics	SUNRISE + SUNSHINE (SEC)	BE HEARD I + BE HEARD II (BKZ q.2.w. or q.4.w.)	
		Before matching	After matching
q.4.w. (N = 360)			
Age, mean (SD)	35.60 (11.55)	36.98 (12.36)	35.60 (11.55)
BMI, mean (SD)	32.40 (7.70)	32.67 (7.85)	32.40 (7.70)
Duration of HS (years), mean (SD)	7.40 (7.60)	8.23 (7.62)	7.40 (7.60)
AN count, mean (SD)	12.95 (8.60)	17.12 (16.72)	12.95 (8.60)
DT count, mean (SD)	2.50 (3.50)	3.78 (4.43)	2.50 (3.50)
Male, %	43.50	40.55	43.50
White, %	79.00	79.73	79.00
Smoking, %	51.50	46.05	51.50
Hurley III, %	36.50	45.02	36.50
Prior biologics, %	22.50	19.24	22.50
Concomitant antibiotics, %	13.00	9.62	13.00
US region, %	15.20	29.90	15.20

AN = abscess and inflammatory nodule; BKZ = bimekizumab; BMI = body mass index; DT = draining tunnel; HS = hidradenitis suppurativa; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SEC = secukinumab; SD = standard deviation; vs. = versus.

Source: Indirect Treatment Comparison Report.⁵⁰

Table 32: Effective Sample Size of BE HEARD by Outcome After Matching to SUNRISE and SUNSHINE

Outcomes (week 48)	BE HEARD I + BE HEARD II (BKZ q.2.w. or q.4.w.)	
	Before matching, N	After matching, ESS (ESS/%N)
q.2.w. (N = 361)		
HiSCR50, HiSCR75, and HiSCR90 (NRI)	292	226 (77.4)
DLQI MCID 5-point reduction (NRI)	227	177 (77.8)
AN50 (NRI)	292	226 (77.4)
q.4.w. (N = 360)		
HiSCR50, HiSCR75, and HiSCR90 (NRI)	292	208 (71.2)
DLQI MCID 5-point reduction (NRI)	227	159 (70.0)
AN50 (NRI)	292	208 (71.2)

AN = abscess and inflammatory nodule; AN50 = $\geq 50\%$ reduction in abscess and inflammatory nodule count; BKZ = bimekizumab; DLQI = Dermatology Life Quality Index; ESS = effective sample size; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HiSCR90 = Hidradenitis Suppurativa Clinical Response 90; MCID = minimal clinically important difference; NRI = nonresponder imputation; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks.

Source: Indirect Treatment Comparison Report.⁵⁰

Table 33: Pooled Baseline Characteristics in BE HEARD Before and After Matching to PIONEER Trials — Base Case

Characteristics	PIONEER I + PIONEER II ADA q.w. (N = 316)	BE HEARD I + BE HEARD II BKZ q.2.w. or q.4.w.	
		Before matching	After matching
Age, mean (SD)	35.53 (10.39)	37.02 (12.41)	35.53 (10.40)
BMI, mean (SD)	32.12 (7.50)	32.72 (7.86)	32.12 (7.50)
AN count, mean (SD)	12.44 (10.12)	17.13 (16.77)	12.45 (10.11)
DT count, mean (SD)	3.77 (4.66)	3.82 (4.44)	3.78 (4.67)
Hs-CRP, mean (SD)	16.69 (21.67)	17.19 (24.18)	16.70 (21.67)
Male, %	37.03	40.28	37.03
White, %	81.96	79.51	81.96
Smoking, %	58.86	45.49	58.85
Hurley stage III, %	47.47	45.14	47.48
Prior biologics, %	0.00	19.79	0.00
US region, %	38.53	30.21	38.54

ADA = adalimumab; AN = abscess and inflammatory nodule; BKZ = bimekizumab; BMI = body mass index; DT = draining tunnel; hs-CRP = high-sensitivity C-reactive protein; q.w. = every week; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation.

Source: Indirect Treatment Comparison Report.⁵⁰

Table 34: Effective Sample Size of the BE HEARD Trial by Outcome After Matching to the PIONEER Trial — Base Case (Bimekizumab vs. Adalimumab Comparison)

Outcomes (week 48)	BE HEARD I + BE HEARD II BKZ q.2.w. or q.4.w.	
	Before matching, N	After matching, ESS (% N)
HiSCR50/HiSCR75/HiSCR90 (LOCF)	292	140 (47.8)

BKZ = bimekizumab; ESS = effective sample size; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HiSCR90 = Hidradenitis Suppurativa Clinical Response 90; LOCF = last observation carried forward; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; vs. = versus.

Source: Indirect Treatment Comparison Report.⁵⁰

Table 35: Overview of MAIC Results for Bimekizumab Every 2 Weeks or Every 4 Weeks vs. Secukinumab Every 2 Weeks and Every 4 Weeks at Weeks 48 to 52

Comparison	HiSCR50 (NRI)		HiSCR75 (NRI)		HiSCR90 (NRI)		DLQI MCID 5-Point Reduction (NRI)	
	ESS	OR (95% CI)	ESS	OR (95% CI)	ESS	OR (95% CI)	ESS	OR (95% CI)
BKZ q.2.w. or q.4.w. vs. SEC q.2.w. and q.4.w.	226	2.00 (1.42 to 2.80) ^a	226	1.91 (1.35 to 2.70) ^a	226	2.05 (1.39 to 3.04) ^a	177	1.49 (1.02 to 2.18) ^a
BKZ q.2.w. or q.4.w. vs. SEC q.2.w. and q.4.w.	208	2.06 (1.45 to 2.92) ^a	208	2.13 (1.49 to 3.05) ^a	208	2.04 (1.36 to 3.04) ^a	159	1.92 (1.29 to 2.87) ^a

BKZ = bimekizumab; CI = confidence interval; BMI = body mass index; DLQI = Dermatology Life Quality Index; ESS = effective sample size; HS = hidradenitis suppurativa; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HiSCR90 = Hidradenitis Suppurativa Clinical Response 90; MAIC = matching-adjusted indirect comparison; MCID = minimal clinically important difference; NRI = nonresponder imputation; OR = odds ratio; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SEC = secukinumab; vs. = versus.

Note: The MAIC was adjusted for sex (% male), race (% white), age, BMI, duration of HS, smoking status (% current smokers), severity (% Hurley stage III), region (% US), draining tunnel count, abscess and inflammatory nodule count, prior biologics (%), and concomitant antibiotics (%).

^aSignificant difference in favour of BKZ.

Source: Indirect Treatment Comparison Report.⁵⁰

Table 36: Overview of MAIC Results for Bimekizumab Every 2 Weeks or Every 4 Weeks vs. Adalimumab Every Week at Week 48

Comparison	HiSCR50 (LOCF)		HiSCR75 (LOCF)		HiSCR90 (LOCF)	
	ESS	OR (95% CI)	ESS	OR (95% CI)	ESS	OR (95% CI)
BKZ q.2.w. or q.4.w. vs. ADA q.w. ^a	140	2.29 (1.30 to 4.05) ^b	140	1.58 (0.92 to 2.72)	140	1.36 (0.77 to 2.42)
BKZ q.2.w. or q.4.w. vs. ADA q.w. (scenario analysis) ^c	239	1.99 (1.19 to 3.32) ^b	239	1.58 (0.97 to 2.61)	239	1.26 (0.73 to 2.14)

ADA = adalimumab; BKZ = bimekizumab; BMI = body mass index; CI = confidence interval; ESS = effective sample size; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HiSCR75 = Hidradenitis Suppurativa Clinical Response 75; HiSCR90 = Hidradenitis Suppurativa Clinical Response 90; hs-CRP = high-sensitivity C-reactive protein; LOCF = last observation carried forward; MAIC = matching-adjusted indirect comparison; OR = odds ratio; q.w. = every week; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; vs. = versus.

^aThe MAIC was adjusted for sex (% male), race (% white), age, BMI, smoking (% current smokers), disease severity (% Hurley stage III), region (% US), draining tunnel count, abscess and inflammatory nodule count, prior biologics (%), and hs-CRP (%).

^bSignificant difference in favour of BKZ.

^cThe MAIC was adjusted for sex (% male), race (% white), smoking (% current smokers), and disease severity (% Hurley stage III).

Source: Indirect Treatment Comparison Report.⁵⁰

Critical Appraisal

Network Meta-Analysis

The clinical SLR conducted in October 2023 identified published literature on RCTs of treatments for HS, of which 9 were suitable for inclusion in the NMAs and MAICs. These trials included adalimumab and secukinumab at approved doses and all doses of bimekizumab. Study selection was based on prespecified, appropriate criteria. Two reviewers completed the study selection, while 1 extracted the data and a second

checked the extraction. Quality assessment was performed by 2 reviewers for each included study. The sponsor's assessment of study quality was that the studies were with low risk of bias except for 1 adalimumab study, which was rated as having "some concerns." No study was excluded based on quality assessment despite there being some concerns about risk of bias in 1 adalimumab study.

The outcomes selected by the sponsor were relevant, although the sponsor did not present results for all outcomes originally targeted in their literature search due to data limitations. The 12- to 16-week time point was relevant for assessing efficacy given the limitations of the trial data, but later time points would have been preferable for generating estimates of long-term efficacy in an NMA.

The networks were star-shaped, and centred on the placebo. There were closed loops within the network, but these belonged to multiarm trials and could not be used to assess consistency.

Some clinical heterogeneity was observed within the study design and trial patient populations. Differences included the time period when the adalimumab trials were conducted, as these were older than the bimekizumab and secukinumab trials and did not recruit any patients who had experience with biologics. Treatment period before crossover or rerandomization also varied between weeks 12 and 16. It is not known which direction these factors would bias the results. Formal heterogeneity testing between studies in the direct analyses showed suggested high statistical heterogeneity (high I^2) in a few of the arms.

One network contained mixed biologic-experienced and biologic-naïve populations (9 trials, $N = 3,129$). Across all 3 treatment arms in the BE HEARD trials, 191 of 1,014 patients (18.8%) had experience with biologics. Across the treatment arms in the SUNRISE and SUNSHINE trials, 255 of 1,084 patients (23.5%) had experience with biologics. The lack of a network containing exclusively patients who were biologic naïve is a weakness of the analyses as there were no relative efficacy estimates for this population. The other network contained biologic-experienced populations.

In the mixed biologic-experienced and biologic-naïve population, several results demonstrated differences favouring bimekizumab over secukinumab and adalimumab, but these findings were not consistent across all outcomes. There were no differences observed for bimekizumab versus comparators for DLQI. The reason for the inconsistency in the dermatology-related quality of life results, compared to the HiSCR, is not clear. The experts consulted for the review suggested that improvement in quality of life may not be fully realized in short-term follow-up. The random-effects models for several outcomes show CIs that cross the null in cases where the fixed-effects models had CIs that did not cross the null. This imprecision in the random-effects models was seen in the results for bimekizumab versus secukinumab and for bimekizumab versus adalimumab. In the case of adalimumab, there were very few outcomes with CIs that did not cross the null, which undermined the sponsor's assertion that bimekizumab is superior to adalimumab.

The results in the biologic-experienced network had wide CIs and only data from 2 outcomes were presented; as such, there was no clearly demonstrated advantage of bimekizumab over secukinumab or adalimumab. The number of studies in either network was not large, particularly for the biologic-experienced population, resulting in wide CIs.

There was little commentary from the sponsor regarding harms, despite the inclusion of SAEs as an outcome of interest. An appendix provided by the sponsor contained some data on SAEs. There was no clear difference in SAE incidence between any of the compared treatments and wide CIs were reported for most of the SAE comparisons.

Matching-Adjusted Indirect Comparison

The sponsor performed an unanchored MAIC because of the lack of a connected treatment network for the week 48 to week 52 time points. This was an adequate justification for performing an MAIC. The selection of comparators was reasonable, according to the clinical experts consulted for this review. The MAIC analyses suggested that there were differences favouring bimekizumab compared to secukinumab, which were seen across several outcomes. However, the results for bimekizumab versus adalimumab across the outcomes were not as consistent as the comparisons with secukinumab.

The sponsor's list of 16 matching variables was reasonable, but there may have been important differences between the studies, and the patient populations in the studies, which were not accounted for. In addition, some of the matching variable data (e.g., prior biologic exposure) was not available for all studies and all outcomes. The base case of the bimekizumab versus secukinumab was adjusted for 12 variables and 11 variables were matched in the bimekizumab-versus-adalimumab MAIC. Study design differences cannot be adjusted for in the MAIC weighting procedures. An MAIC generates results that estimate the relative treatment effect in the population matched to the comparator trial rather than the other way around, which leads to questions about the generalizability of the findings.

The sponsor did attempt to use prior biologic exposure as a matching variable, but there were no analyses in the MAIC that analyzed an exclusively biologic-naïve population or an exclusively biologic-experienced population.

In the MAIC analyses, the effective sample size for the bimekizumab group was reduced to 70% from 77% for the comparison to secukinumab, and to 46% from 47% for the comparison to adalimumab. The scaled weights did not have any extreme weights, an indicator of good overlap (in measured variables) between the population.

Discussion

Summary of Available Evidence

Two double-blind, placebo-controlled, phase III RCTs, the BE HEARD I (N = 505) and BE HEARD II (N = 509) trials, evaluated the efficacy and safety of bimekizumab compared to placebo in adults (aged 18 years and older) with a clinically verifiable diagnosis of moderate to severe HS for at least 6 months before the baseline visit. All patients had a history of inadequate response, intolerance, or contraindication to systemic antibiotics used for treating HS. In both trials, the primary outcome was the proportion of patients with achieved HiSCR50 at week 16. Key secondary outcomes of interest for this review included change from baseline in the DLQI total score and worst skin pain responder rate (based on a clinical meaningful

benefit at week 16) using the HSSDD. An additional key outcome of clinical importance was the proportion of patients who experienced a flare by week 48, which was an exploratory outcome investigated in both trials. Key exclusion criteria included prior treatment with an IL-17 biologic response modifier without an appropriate washout period, a draining tunnel count greater than 20 at baseline, the use of prescription topical therapy for HS within 14 days before the baseline study visit, and the presence of any other active skin condition that could interfere with HS assessment (i.e., sarcoidosis, systemic lupus erythematosus), active IBD, and/or a primary immunosuppressive condition.

Both trials were completed in 3 study periods: an initial screening period, to ensure that the enrolled patients met the eligibility criteria; a 48-week treatment period; and a 20-week safety period designed for posttreatment follow-up. The treatment period comprised a double-blind, placebo-controlled initial treatment period (week 0 to 16), followed by a double-blind, 32-week maintenance treatment period (week 16 to 48), during which all patients received bimekizumab. Patients were randomized (2:2:2:1) in both studies to receive bimekizumab 320 mg every 2 weeks from week 0 to 48; bimekizumab 320 mg every 4 weeks from week 0 to 48; bimekizumab 320 mg every 2 weeks from week 0 to 16 and then bimekizumab 320 mg every 4 weeks from week 16 to 48; or placebo until week 16, and then bimekizumab 320 mg every 2 weeks from week 16 to 48. The recommended dosing approved by Health Canada is bimekizumab 320 mg every 2 weeks for the first 16 weeks, followed by bimekizumab 320 mg every 4 weeks thereafter. This report summarizes pooled data from the 2 groups that received bimekizumab 320 mg every 2 weeks during the initial treatment period, which were formally compared to the data from the placebo group at week 16. In addition, data from the 2 groups that switched regimens for the maintenance treatment period are presented as supporting longer-term evidence from week 16 to 48; these groups are the one that switched from placebo to bimekizumab 320 mg every 2 weeks and the one that switched from bimekizumab 320 mg every 2 weeks to every 4 weeks for the maintenance treatment period.

The mean age of patients ranged from 36.4 years (SD = 12.4 years) in the BE HEARD I trial placebo group to 38.1 years (SD = 13.2 years) in the BE HEARD II trial placebo group. At baseline, most patients were diagnosed with Hurley stage II (derived) disease severity, from 47.2% (34 of 72 patients) in the placebo group in the BE HEARD I trial to 60.8% in both the bimekizumab 320 mg every 2 weeks (177 of 291 patients) and the placebo (45 of 74 patients) groups in the BE HEARD II trial. Mean disease duration ranged from 7.4 years in the bimekizumab group in the BE HEARD II trial to 11.5 years in the placebo group of the BE HEARD I trial. In the BE HEARD I trial, most patients across both groups were female (60.9% in the bimekizumab group and 61.1% in the placebo group), whereas in the BE HEARD II trial, 51.5% of the bimekizumab group was female versus 41.9% in the placebo group.

In the absence of evidence comparing bimekizumab with available active comparators, the sponsor submitted indirect evidence in the form of an NMA (outcomes from weeks 12 to 16) and an MAIC (outcomes from weeks 48 to 52). The NMA assessed the efficacy of bimekizumab relative to adalimumab and secukinumab from weeks 12 to 16 and was conducted using a Bayesian approach, informed by 9 RCTs (N = 3,129). Two networks were presented, 1 containing mixed biologic-experienced and biologic-naïve populations and the other containing biologic-experienced populations. Due to the lack of a connected

treatment network for the week 48 to week 52 time points, the sponsor performed an unanchored MAIC with 16 matching variables.

Interpretation of Results

Efficacy

HS is a chronic, debilitating inflammatory disease with no cure, and the clinical experts consulted for this review emphasized that treatment response to currently available treatment options in real-world clinical practice is variable; even after initial improvement, some patients may experience a treatment response plateau (especially those with extensive disease progression) or loss (particularly those receiving anti-TNF therapy). The patient groups, clinician groups, and clinical experts noted the need for treatments that are safe and effective in managing HS (i.e., they reduce lesions or flares and pain) and that lead to disease remission. Some key goals highlighted by the experts consulted during the review of HS management in current practice included pain reduction, minimizing drainage, prevention of new lesions or flares, and slowing or halting disease progression.

The primary outcome in the BE HEARD I and BE HEARD II trials was HiSCR50 at week 16, defined as a reduction in total AN count of at least 50% from baseline, with no increase from baseline in the number of abscesses and/or draining tunnels. The HiSCR50 is a validated, disease-specific outcome that reflects a change in disease activity and response to treatment for HS. In both trials, treatment with bimekizumab 320 mg administered every 2 weeks resulted in a greater proportion of patients with an HiSCR50 response at 16 weeks relative to placebo. Between-group treatment differences in both trials were considered clinically meaningful (18.15% [95% CI, 6.31% to 29.98%] and 19.61% [95% CI, 7.50% to 31.72%] in favour of bimekizumab in the BE HEARD I and BE HEARD II trials, respectively). However, the 95% CIs included values less than the 10% threshold deemed clinically important by the experts consulted by CDA-AMC, indicating the possibility of no difference between groups. Sensitivity analyses in both trials were consistent with the primary analyses. While statistically significant, the observed responder rate was lower than the initial assumption used in the sample size calculation, and the placebo response rates were higher. This would have produced a smaller observed treatment effect and possibly reduced the precision of the estimates despite an initial 99% power. Overall, bimekizumab 320 mg every 2 weeks likely results in a clinically meaningful increase in the proportion of patients with HiSCR50 response when compared with placebo. In the BE HEARD I and II trials, HiSCR75 results were consistent with those of HiSCR50 at week 16, demonstrating between-group treatment differences of 15.35% (95% CI, 3.71% to 27.00%) and 20.57% (95% CI, 9.89% to 31.26%), respectively. The proportion of HiSCR75 responders was slightly lower compared to HiSCR50 in the BE HEARD I and II trials for both the bimekizumab 320 mg every 2 weeks group and the placebo group.

Flare rate, defined as a minimum 25% increase in AN count with an absolute increase greater than or equal to 2 AN counts relative to baseline, was identified by the experts as a clinically meaningful outcome for patients with HS. The experts emphasized that a key goal of HS treatment involves reducing the frequency and robustness of flares. In the BE HEARD II trial, flare by week 16 was included as a ranked secondary outcome, but did not achieve statistical significance. The clinical experts noted that the goal in real-world

practice is to reduce flares over time, and that it is challenging to assess a reduction in the rate of flares over an observation period of less than a year; as such, flare by week 48 was considered more clinically relevant than the assessment at week 16. In both studies, flare by week 48 was presented descriptively due to a lack of a comparator group in the maintenance treatment period. During the initial and maintenance treatment periods of the BE HEARD I and II trials, the proportion of patients who experienced a flare by week 48 in the bimekizumab 320 mg every 2 weeks or every 4 weeks group was at 55.9% and 51.2%, respectively. However, due to the identified data limitations at week 48 (potential missing data in the maintenance period) and uncertainty in the estimates, the evidence is very uncertain about the effect of bimekizumab (320 mg every 2 weeks to week 16, followed by every 4 weeks from week 16 to 48) on flare rate when compared with any comparator as all patients were switched to bimekizumab and therefore, there was no evidence relative to an appropriate comparator at this time. The experts consulted by CDA-AMC noted that HS inflammatory lesions usually take time to subside, even when patients are receiving therapy, and that patients still experience fluctuations in disease (flares) that are a result of lifestyle factors such as stress and dietary triggers.

The clinical experts, patient groups, and clinician groups providing input for this review also highlighted improvement in quality of life as an important treatment goal. The experts noted that aside from disease progression, patient outcomes are useful in assessing HRQoL because chronic scarring can prevent full assessment of disease clearance following treatment. While both trials included several patient-reported HRQoL evaluations (DLQI, HiSQoL, EQ-5D-3L visual analogue scale), only change from baseline in DLQI total score was assessed as a key ranked secondary end point at week 16 in the BE HEARD I and II trials. Further, the DLQI was identified as the most clinically relevant assessment of HRQoL in the trials due to clinician familiarity and common use in dermatology trials, and it was therefore included as a key outcome in this review. The DLQI is a skin disease-specific questionnaire that evaluates the effect of symptoms and treatment on patient quality of life over a 7-day recall period. The DLQI MID in both trials was 4 points, which is consistent with previous dermatology studies (not specific to HS).^{42,47} In the BE HEARD I trial, the treatment difference for change from baseline in DLQI total score at week 16 between bimekizumab 320 mg every 2 weeks and placebo did not reach the 4-point threshold, suggesting little to no clinically meaningful benefit in HRQoL compared to placebo despite statistical significance being achieving in favour of bimekizumab; however, the 97.5% CI in the BE HEARD I trial did include the 4-point threshold, suggesting the potential for important benefit. In the BE HEARD II trial, the point estimate and 97.5% CI for the between-group difference did not include the potential for important benefit based on the 4-point MID. The findings were consistent with those in the BE HEARD I trial, suggesting little to no clinically meaningful treatment difference. Further, the previous ranked secondary end point did not meet statistical significance and thus statistical significance for the end-point change from baseline in DLQI total score at week 16 could not be interpreted. Because missing data and imprecision were limitations observed for this outcome in both trials, treatment with bimekizumab 320 mg every 2 weeks likely results in little to no clinically meaningful difference in change from baseline in DLQI total score at week 16 when compared with placebo. It is important to reiterate the patient group feedback highlighting the profoundly negative impact of HS on HRQoL. Taking this into consideration, it is unlikely that a clinically meaningful response to treatment would be observed after 16 weeks of improvement. Further, although the MID has been validated for other dermatologic conditions,

it is not specific to HS; this is a limitation of this assessment that contributes to the low certainty of the between-group results. HiSQOL was included in both the BE HEARD I and II trials as an exploratory end point (but was not included in the statistical hierarchy) as an additional measure of HRQoL specific to HS. A meaningful within-patient MID for the change from baseline in HiSQOL total score of a minimum 20-point reduction was noted. However, like DLQI, the mean change from baseline in HiSQOL total score in both treatment groups did not achieve clinical significance.

The clinical experts, as well as patient groups and clinician groups, identified symptom reduction (particularly improved pain management) as a key goal of HS treatment and a top priority for patients. Symptom severity was assessed using the HSSDD, a patient-reported outcome that evaluates patient perception of the main HS symptoms over a 24-hour recall period. Skin pain response was assessed as a key ranked secondary end point at week 16 in both the BE HEARD I and BE HEARD II trials. Response was defined as at least a 3-point reduction from baseline in HSSDD worst pain score, among BE HEARD participants with a score greater than or equal to 3 at baseline, based on weekly averages.⁴⁹ In the BE HEARD I trial, there was no statistically significant difference in the proportion of patients with skin pain response between the bimekizumab treatment and placebo groups, while in the BE HEARD II trial, a previous ranked secondary end point did not meet statistical significance, and therefore significance could not be interpreted. In the BE HEARD trials, the between-group risk difference did not meet the minimum 25% to 50% threshold that was deemed clinically meaningful by the consulted experts; however, the 95% CI included the potential for important benefit. As there is no published consensus on this threshold, it was informed by expert input for the purposes of this review. Missing data for this end point were a concern for both precision and risk of bias, and the trial randomization did not stratify for HSSDD score greater than or equal to 3 at baseline, leading to potential bias due to confounding. The risk of bias due to missing data and imprecision were considered limitations for this outcome in both trials, and it was concluded with low certainty that bimekizumab 320 every 2 weeks may result in little to no difference in worst skin pain response rate (measured using the HSSDD) at week 16, when compared with placebo.

Because HS is a chronic inflammatory disease with no cure, long-term data beyond week 16 are needed to assess the comparative effectiveness of bimekizumab against placebo and to evaluate sustained responses among patients with HS. While the BE HEARD trials provided estimates beyond week 16 for key primary and secondary outcomes of importance to HS management, these data had limitations, namely, the absence of an appropriate active comparator, as patients receiving placebo switched to treatment with bimekizumab during the maintenance treatment period from week 16 to 48, as well as concerns regarding missing data at these time points. In addition, some exclusions in the study population present a limitation to the generalizability of the trial findings. Patients with certain chronic autoimmune disorders, notably systemic lupus erythematosus, were excluded from the BE HEARD trials. The clinical experts indicated that some of the patients for whom anti-TNF therapy is contraindicated may instead benefit from bimekizumab treatment. Given the high prevalence of comorbidities in HS, these exclusions limit the applicability of the findings to a broader, more complex patient population. In addition, patients with draining tunnel counts greater than 20 at baseline were excluded from both trials. The clinical experts noted that these individuals would still be considered for treatment with bimekizumab, as they tend to have considerably more severe

disease and usually require monotherapy alongside surgery for optimal HS management. The experts indicated that bimekizumab treatment could help reduce disease severity, potentially decreasing the extent of the necessary surgery and postoperative care requirements. Lastly, the variable treatment response observed in the bimekizumab group versus placebo is expected, according to the experts; extensive disease before enrolment may have impacted treatment responses, as some patients may not experience complete resolution of scarring despite the new treatment preventing disease progression. Direct comparative evidence for bimekizumab was limited to the 2 placebo-controlled trials. Relevant comparators for this review included secukinumab and adalimumab, although the experts noted that the use of placebo for assessing efficacy and safety of bimekizumab was appropriate as this is consistent with other studies in the HS setting. To address this gap in the evidence, the sponsor submitted indirect evidence with comparisons to secukinumab and adalimumab in the form of an NMA and an MAIC. The NMA included outcomes assessed at week 12 to 16, and the MAIC was used to evaluate outcomes assessed at weeks 48 to 52. Results for the HiSCR50, the primary outcome in the BE HEARD trials, were considered a key outcome of interest from the NMA. The HiSCR75, HiSCR90, and HiSCR100 were reported to support the pharmacoeconomic analysis. Results of the sponsor's NMA and MAIC showed differences between bimekizumab and secukinumab in the mixed population of patients who were biologic naive and biologic experienced for some efficacy outcomes. These differences favoured bimekizumab over secukinumab for the HiSCR50 in the fixed-effects model, as well as the HiSCR75, the HiSCR90, and the HiSCR100. Due to the methodological limitations of the NMA and MAIC analyses and the fact that the results had 95% CrIs that crossed the null in several of the random-effects models, the magnitude of benefit for bimekizumab versus secukinumab remains uncertain. The clinical experts expected that bimekizumab would perform similarly or better when compared to adalimumab based on experience in treating psoriasis; however, in the indirect comparison, there was uncertainty around the point estimates for the comparisons of bimekizumab and adalimumab, and no clear indication of a difference between bimekizumab and adalimumab. More specifically, the uncertainty is due to imprecision resulting from the 95% CrI for HiSCR50 that includes the possibility of no difference between bimekizumab and adalimumab, as well as the timing of the clinical trials and potential for differences in assessments based on evolving clinical practice. Although not aligned with the key outcomes identified for this review, the outcomes for flares, reduction in worst skin pain (numerical rating scale 30), and the proportion of patients with a 5-point reduction in the DLQI, were also reported as supportive evidence in the context of this review. None of the analyses at week 12 to 16 supported a difference between bimekizumab and secukinumab or adalimumab based on these outcomes. Lastly, results of the MAIC at weeks 48 to 52 were also reported and are supportive of the results at weeks 12 to 16; however, the data up to week 48 were subject to limitations similar to those described for the pivotal trials and to limitations associated with the MAIC, such as the generalizability of the findings.

Harms

All notable harms of interest identified by the clinical experts, patient groups, clinician groups, and public drug plans are summarized in this report. However, only the notable harms included in [Table 6](#) were assessed using GRADE. Oral candidiasis was identified as a key harm of interest by the clinical experts, as bimekizumab was associated with oral candidiasis when used for other dermatological conditions. The

experts indicated that long-term assessment (> 6 months) would be meaningful considering that HS is a lifelong disease.

In the BE HEARD I and BE HEARD II trials, respectively, 67.1% and 64.5% of patients in the pooled bimekizumab every 2 weeks group experienced 1 or more TEAEs during the initial treatment period, compared with 66.7% and 56.8% of patients in the respective placebo groups. The proportion of SAEs reported during the initial treatment period in both trials was generally low in the pooled bimekizumab 320 mg every 2 weeks group (2.8% and 3.1%, respectively, for the BE HEARD I and BE HEARD II trials) versus no reports of SAEs in the placebo group. The proportion of patients who stopped treatment due to AEs in the first 16 weeks was also low (3.5% in the pooled bimekizumab 320 mg every 2 weeks group and 1.4% in the placebo group of the BE HEARD I trial, and 4.1% in the bimekizumab 320 mg every 2 weeks group in the BE HEARD II trial; no patients in the BE HEARD II trial placebo group discontinued the study treatment). Overall, while the lack of active comparator and long-term data were identified as study limitations in both trials, no major safety signals with bimekizumab treatment were observed up to week 48.

Oral candidiasis was a key harm identified by the experts consulted for this review. In the initial treatment period, oral candidiasis was reported in the pooled bimekizumab 320 mg every 2 weeks group in both the BE HEARD I trial (5.9% of patients) and the BE HEARD II trial (8.3% of patients) trials, while no patients receiving placebo reported oral candidiasis in either study, suggesting that bimekizumab likely results in an increase in the proportion of patients with oral candidiasis relative to placebo. In the overall treatment period, oral candidiasis was reported in all groups that received bimekizumab 320 mg; however, it is not possible to draw conclusions from the longer-term evidence due to the lack of an active comparator arm.

The clinical experts indicated that, overall, the AEs (including oral candidiasis) reported in both treatment periods across both trials were expected and usually clinically manageable with no meaningful consequences. The experts indicated that treatment selection would be made on a case-by-case basis, weighing benefits against harms according to each patient's circumstance. No new safety signals were reported in either trial. No assessments of relative harms were performed in the NMA or MAIC, and therefore the relative risk of harm of bimekizumab versus secukinumab or adalimumab is not known.

Conclusion

Collectively, the evidence from the BE HEARD I (N = 505) and BE HEARD II (N = 509) studies demonstrated that 16 weeks of treatment with bimekizumab 320 mg every 2 weeks likely results in a clinically meaningful improvement in HS inflammatory lesions (as measured by HiSCR50 response) when compared to placebo, in patients aged 18 years and older with moderate to severe HS. Improving quality of life and pain were identified by clinicians and patients as important treatment goals for patients living with HS, and the change from baseline to week 16 in the DLQI total score and worst skin pain responder rate (measured using the HSSDD) were included as key secondary outcomes in the BE HEARD trials. The reported between-group differences were assessed with low certainty, suggesting that bimekizumab 320 mg every 2 weeks may result in little to no clinically meaningful difference, when compared with placebo. Of note, the assessment

of HRQoL based on the DLQI was limited by an MID that is not specific to HS and an assessment at 16 weeks that is likely too soon to expect a clinically meaningful improvement. There was also a high level of uncertainty as to whether bimekizumab 320 mg reduces the proportion of patients experiencing a flare by week 48 because of the lack of a comparator during the maintenance treatment period. The results from the sponsor-conducted NMA (weeks 12 to 16) and MAIC (weeks 48 to 52) suggest that bimekizumab may have advantages over secukinumab in treating HS inflammatory lesions (as measured by HiSCR50 response) in patients with HS who are biologic naive or biologic experienced, but methodological limitations and inconsistent results across models result in the magnitude of benefit being uncertain. Indirect comparisons provided no clear indication of a difference between bimekizumab and adalimumab. No new concerns with the harms of bimekizumab were identified based on the harms data observed with treatment for up to 48 weeks across the BE HEARD trials. The number of SAEs and the proportion of patients who discontinued study treatment due to AEs were low, and no deaths were reported. Notable harms, such as oral candidiasis, were aligned with expectations for bimekizumab and considered manageable in clinical practice with no meaningful consequences. In the absence of a comparator group for the week-48 follow-up time point, it is not possible to draw definitive conclusions about the long-term efficacy or harms of bimekizumab versus any comparator, including placebo.

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Appendix 1: Detailed Outcome Data

Please note that this appendix has not been copy-edited.

BE HEARD I and BE HEARD II

Table 37: Concomitant Medications Used by at Least 5% of Study Patients in Any Treatment Group in the Initial Treatment Period — BE HEARD I and BE HEARD II

Concomitant medication, n (%)	BE HEARD I		BE HEARD II	
	Bimekizumab 320 mg q.2.w. (N = 286)	Placebo (N = 72)	Bimekizumab 320 mg q.2.w. (N = 290)	Placebo (N = 74)
Any concomitant medications, n (%)	251 (87.8)	60 (83.3)	230 (79.3)	58 (78.4)
Alimentary tract and metabolism	97 (33.9)	26 (36.1)	88 (30.3)	20 (27.0)
Metformin	19 (6.6)	6 (8.3)	7 (2.4)	2 (2.7)
Metformin hydrochloride	3 (1.0)	1 (1.4)	14 (4.8)	1 (1.4)
Omeprazole	17 (5.9)	4 (5.6)	NR	NR
Cholecalciferol	15 (5.2)	4 (5.6)	NR	NR
Anti-infectives for systemic use	148 (51.7)	33 (45.8)	119 (41.0)	25 (33.8)
Fluconazole	20 (7.0)	0	18 (6.2)	0
Amoxicillin trihydrate; clavulanate potassium	10 (3.5)	5 (6.9)	NR	NR
Doxycycline	24 (8.4)	8 (11.1)	23 (7.9)	5 (6.8)
Tozinameran	57 (19.9)	15 (20.8)	36 (12.4)	11 (14.9)
COVID-19 vaccine mRNA (MRNA1273)	19 (6.6)	5 (6.9)	NR	NR
Genitourinary system and sex hormones	79 (27.6)	15 (20.8)	69 (23.8)	11 (14.9)
Levonorgestrel	8 (2.8)	4 (5.6)	NR	NR
Ethinylestradiol; levonorgestrel	NR	NR	9 (3.1)	1 (1.4)
Drospirenone; ethinylestradiol	NR	NR	5 (1.7)	2 (2.7)
Musculoskeletal system	71 (24.8)	20 (27.8)	68 (23.4)	16 (21.6)
Ibuprofen	47 (16.4)	10 (13.9)	39 (13.4)	10 (13.5)
Nervous system	134 (46.9)	31 (43.1)	91 (31.4)	25 (33.8)
Paracetamol	61 (21.3)	20 (27.8)	28 (9.7)	10 (13.5)
Respiratory system	59 (20.6)	16 (22.2)	NR	NR
Salbutamol	16 (5.6)	5 (6.9)	NR	NR

Concomitant medication, n (%)	BE HEARD I		BE HEARD II	
	Bimekizumab 320 mg q.2.w. (N = 286)	Placebo (N = 72)	Bimekizumab 320 mg q.2.w. (N = 290)	Placebo (N = 74)
Systemic hormonal preparations, excluding sex hormones and insulins	NR	NR	21 (7.2)	9 (12.2)
Levothyroxine sodium	NR	NR	9 (3.1)	4 (5.4)

MRNA = messenger ribonucleic acid; NR = not reported; q.2.w. = every 2 weeks.

Note: Concomitant medications were any medications that had a start date on or after the start date of drug under investigation, or any medications that had a start date on or before the last dose of drug under investigation + 28 days (whether placebo or bimekizumab). Only medications that were initiated before the week-16 visit are included in this summary. This includes medications that started before the initial treatment period and those that continued into the maintenance treatment period.

Note: Patients were randomized at baseline to 1 of 4 treatment sequences, with treatment switched after the initial treatment period for the placebo or bimekizumab 320 mg q.2.w. group and the bimekizumab 320 mg q.2.w. or q.4.w. group, at week 16. Patients' data were summarized according to randomized treatment as allocated at baseline.

Note: Patients receiving bimekizumab 320 mg q.2.w. were pooled from the bimekizumab 320 mg q.2.w./q.2.w. and bimekizumab 320 mg q.2.w. or q.4.w. groups.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 38: Concomitant Medications Used by at Least 5% of Study Patients in Any Treatment Group in the Maintenance Treatment Period — BE HEARD I and BE HEARD II

Concomitant medication, n (%)	BE HEARD I		BE HEARD II	
	Bimekizumab 320 mg q.2.w. or q.4.w. (N = 129)	Placebo/ bimekizumab 320 mg q.2.w. (N = 65)	Bimekizumab 320 mg q.2.w. or q.4.w. (N = 130)	Placebo/ bimekizumab 320 mg q.2.w. (N = 69)
Any concomitant medications, n (%)	115 (89.1)	62 (95.4)	119 (91.5)	58 (84.1)
Alimentary tract and metabolism	50 (38.8)	31 (47.7)	55 (42.3)	29 (42.0)
Metformin	5 (3.9)	4 (6.2)	NR	NR
Metformin hydrochloride	NR	NR	6 (4.6)	1 (1.4)
Omeprazole	10 (7.8)	5 (7.7)	NR	NR
Pantoprazole sodium sesquihydrate	4 (3.1)	5 (7.7)	NR	NR
Nystatin	8 (6.2)	3 (4.6)	8 (6.2)	3 (4.3)
Cholecalciferol	7 (5.4)	4 (6.2)	NR	NR
Anti-infectives for systemic use	82 (63.6)	48 (73.8)	97 (74.6)	41 (59.4)
Fluconazole	16 (12.4)	5 (7.7)	17 (13.1)	2 (2.9)
Amoxicillin trihydrate; clavulanate potassium	11 (8.5)	3 (4.6)	8 (6.2)	3 (4.3)
Amoxicillin	9 (7.0)	4 (6.2)	3 (2.3)	1 (1.4)
Clindamycin	2 (1.6)	4 (6.2)	NR	NR
Cefalexin	4 (3.1)	4 (6.2)	NR	NR
Doxycycline	13 (10.1)	10 (15.4)	15 (11.5)	6 (8.7)
Tozinameran	32 (24.8)	15 (23.1)	39 (30.0)	25 (36.2)
COVID-19 vaccine MRNA (MRNA1273)	17 (13.2)	6 (9.2)	11 (8.5)	6 (8.7)

Concomitant medication, n (%)	BE HEARD I		BE HEARD II	
	Bimekizumab 320 mg q.2.w. or q.4.w. (N = 129)	Placebo/ bimekizumab 320 mg q.2.w. (N = 65)	Bimekizumab 320 mg q.2.w. or q.4.w. (N = 130)	Placebo/ bimekizumab 320 mg q.2.w. (N = 69)
Influenza vaccine	5 (3.9)	3 (4.6)	NR	NR
Cardiovascular system	30 (23.3)	14 (21.5)	31 (23.8)	23 (33.3)
Amlodipine	5 (3.9)	0	NR	NR
Dermatologicals	55 (42.6)	29 (44.6)	40 (30.8)	26 (37.7)
Mupirocin	8 (6.2)	2 (3.1)	NR	NR
Ketoconazole	1 (0.8)	3 (4.6)	3 (2.3)	3 (4.3)
Triamcinolone acetonide	7 (5.4)	3 (4.6)	NR	NR
Triamcinolone	3 (2.3)	8 (12.3)	NR	NR
Genitourinary system and sex hormones	39 (30.2)	17 (26.2)	34 (26.2)	15 (21.7)
Levonorgestrel	3 (2.3)	4 (6.2)	NR	NR
Dienogest; ethinylestradiol	1 (0.8)	4 (6.2)	NR	NR
Drospirenone; ethinylestradiol	NR	NR	3 (2.3)	2 (2.9)
Ethinylestradiol; levonorgestrel	NR	NR	5 (3.8)	0
Musculoskeletal system	43 (33.3)	25 (38.5)	33 (25.4)	19 (27.5)
Ibuprofen	29 (22.5)	15 (23.1)	20 (15.4)	10 (14.5)
Naproxen	7 (5.4)	3 (4.6)	NR	NR
Nervous system	70 (54.3)	34 (52.3)	39 (30.0)	26 (37.7)
Paracetamol	36 (27.9)	23 (35.4)	16 (12.3)	10 (14.5)
Respiratory system	30 (23.3)	24 (36.9)	NR	NR
Salbutamol	7 (5.4)	4 (6.2)	NR	NR
Cetirizine hydrochloride	4 (3.1)	2 (3.1)	NR	NR
Systemic hormonal preparations, excluding sex hormones and insulins	NR	NR	12 (9.2)	9 (13.0)
Levothyroxine sodium	NR	NR	6 (4.6)	5 (7.2)

MRNA = messenger ribonucleic acid; NR = not reported; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks.

Notes: Concomitant medications were any medications that had a start date on or after the start date of drug under investigation, or any medications that had a start date on or before the last dose of drug under investigation + 28 days (whether placebo or bimekizumab). Only medications that were taken at least once after week 16 are included in this summary. This includes medications that started before the maintenance treatment period.

Patients were randomized at baseline to 1 of 4 treatment sequences, with treatment switched after the initial treatment period for the placebo or bimekizumab 320 mg q.2.w. group and the bimekizumab 320 mg q.2.w. or q.4.w. groups, starting at week 16. Patients' data were summarized according to randomized treatment as allocated at baseline.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 39: Key Efficacy Outcomes at Week 48 (Maintenance Treatment Period, Randomized Set)

Outcome	BE HEARD I		BE HEARD II	
	BKZ 320 mg q.2.w. or q.4.w. (N = 146)	Placebo/BKZ 320 mg q.2.w. (N = 72)	BKZ 320 mg q.2.w. or q.4.w. (N = 146)	Placebo/BKZ 320 mg q.2.w. (N = 74)
HiSCR50 responder rate^a				
Week 48 responder rate, % (95% CI)	40.2 (31.7 to 48.7)	31.7 (20.3 to 43.1)	44.5 (36.0 to 53.0)	55.8 (44.0 to 67.6)
n/Nsub (%)	83/104 (79.8)	29/44 (65.9)	87/107 (81.3)	45/61 (73.8)
Flare rate				
Flare rate by week 48, % (95% CI)	55.9 (47.6 to 64.3)	69.9 (59.0 to 80.7)	51.2 (42.9 to 59.4)	37.9 (26.6 to 49.2)
n/Nsub (%)	27/144 (18.8)	25/71 (35.2)	26/145 (17.9)	16/73 (21.9)
Change from baseline in DLQI total score^b				
Baseline, mean (SE)	11.0 (0.6)	12.5 (0.9)	10.5 (0.6)	12.2 (0.7)
Change from baseline at week 48, mean (SE)	-5.0 (0.6)	-6.1 (1.2)	-5.4 (0.6)	-6.7 (0.8)
HSSDD worst skin pain responder rate based on clinically meaningful within-patient change				
Week 48 responder rate, % (95% CI)	NR	NR	NR	NR
n/Nsub (%)	NR	NR	NR	NR

BKZ = bimekizumab; CI = confidence interval; DLQI = Dermatology Life Quality Index; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50; HSSDD = Hidradenitis Suppurativa Symptom Daily Diary; NR = not reported; OC = observed case; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SE = standard error.

Note: In the n/Nsub (%) row (OC analysis), Nsub represents the number of patients with a nonmissing measurement at week 16, and percentages were calculated accordingly (i.e., where data recorded after an intercurrent event were included as recorded).

^aIntermittent missing data are imputed using multiple imputation with Markov Chain Monte Carlo (MCMC) method followed by monotone regression for monotone missing data. Lesion counts are imputed and then dichotomized to obtain the response status. Participants who experience an intercurrent event are treated as nonresponders following the intercurrent event.

^bIntermittent missing data are imputed using multiple imputation with Markov Chain Monte Carlo (MCMC) method followed by monotone regression for monotone missing data. Participants who experience an intercurrent event are treated as missing following the intercurrent event and imputed using the multiple imputation method for missing data.

Sources: BE HEARD I Clinical Study Report;¹⁶ BE HEARD II Clinical Study Report.¹⁷ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Indirect Evidence

Table 40: Summary of Studies Identified in the NMA

Study	Trial design	Length of initial double-blind period (weeks)	Total length of follow-up (weeks)	Treatment arms	N	Trt change after double-blind period?
BKZ						
HS0001	Phase II, double-blind, multicentre,	12	30	BKZ: 640 mg at baseline followed by 320 mg q.2.w.	46	No

Study	Trial design	Length of initial double-blind period (weeks)	Total length of follow-up (weeks)	Treatment arms	N	Trt change after double-blind period?
	international RCT					
				ADA: 160-mg at baseline, 80 mg at week 2 followed by 40 mg q.w. (weeks 4 to 10)	22	No
				PBO: Baseline, week 2, q.w. (weeks 4 to 10)	22	No
BE HEARD I	Phase III, double-blind, multicentre, international RCT	16	48	BKZ: 320 mg q.2.w. at weeks 0 to 48	143	No
				BKZ: 320 mg q.2.w. at weeks 0 to 16, then BKZ: 320 mg q.4.w. at weeks 17 to 48	146	Yes
				BKZ q.4.w.: 320 mg q.4.w. at weeks 0 to 48	144	No
				PBO/BKZ q.2.w.: PBO at weeks 0 to 16, then BKZ 320 mg q.2.w. at weeks 17 to 48	72	Yes
BE HEARD II	Phase III, double-blind, multicentre, international RCT	16	48	BKZ q.2.w.: 320 mg q.2.w. at weeks 0 to 48	145	No
				BKZ: 320 mg q.2.w. at weeks 0 to 16, then BKZ: 320 mg q.4.w. at weeks 17 to 48	146	Yes
				BKZ q.4.w.: 320 mg q.4.w. at weeks 0 to 48	144	No
				PBO/BKZ: PBO at weeks 0 to 16, then BKZ 320 mg q.2.w. at weeks 17 to 48	74	Yes
ADA						
PIONEER I	Phase III, double-blind, multicentre, international RCT	12	36 + 132-week OLE study (pooled with PIONEER II)	ADA: 160 mg at week 0, 80 mg at week 2, followed by 40 mg q.w. (weeks 4 to 12), then patients were rerandomized after week	153	Yes

Study	Trial design	Length of initial double-blind period (weeks)	Total length of follow-up (weeks)	Treatment arms	N	Trt change after double-blind period?
				12 to receive either PBO q.w., ADA q.w. or ADA q.2.w. (weeks 12 to 35)		
				PBO: At week 0, week 2, followed by q.w. (weeks 4 to 12) then ADA (160 mg at week 12, 80 mg at week 14 and 40 mg q.w. [weeks 16 to 35])	154	Yes
PIONEER II	Phase III, double-blind, multicentre, international RCT	12	36 + 132-week OLE study (pooled with PIONEER I)	ADA: 160 mg at week 0, 80 mg at week 2, followed by 40 mg q.w. (week 4 to 12) then patients were rerandomized after week 12 to receive either PBO q.w., ADA q.w. or ADA q.2.w. (weeks 12 to 35)	163	Yes
				PBO: At week 0, week 2, followed by q.w. (weeks 4 to 35)	163	No
NCT00918255	Phase II, double-blind, multicentre, international RCT	16	52 + 36-week OLE study	ADA: 160 mg at week 0, 80 mg at week 2, followed by 40 mg q.w. (weeks 4 to 15) then patients received ADA 40 mg q.2.w. (weeks 16 to 52)	51	Yes
				PBO: q.w. (weeks 0 to 15) then patients received ADA 40 mg q.2.w. (weeks 16 to 52)	51	Yes
SHARPS	Phase IV, double-blind, multicentre, international RCT	12	24	ADA and surgery: 160 mg at week 0, 80 mg at week 2, followed by 40 mg q.w. up to week 23	103	Yes (surgery at week 13)
				PBO and surgery: PBO at week 0, week 2, followed by q.w. up to week 23	103	Yes (surgery at week 13)
SEC						
SUNRISE	Phase III, double-blind, multicentre, international RCT	16	52	SEC: 300 mg q.w. (weeks 0 to 4), followed by 300 mg q.2.w. (up to week 52)	180	No

Study	Trial design	Length of initial double-blind period (weeks)	Total length of follow-up (weeks)	Treatment arms	N	Trt change after double-blind period?
SUNSHINE	Phase III, double-blind, multicentre, international RCT	16	52	SEC: 300 mg q.w. (weeks 0 to 4), followed by 300 mg q.4.w. (up to week 52)	180	No
				PBO q.w. (weeks 0 to 4), followed by PBO q.2.w. (weeks 4 to 16) then SEC q.2.w. or q.4.w. (up to week 52)	183	Yes
				SEC: 300 mg q.w. (weeks 0 to 4), followed by 300 mg q.2.w. (up to week 52)	181	No
				SEC: 300 mg q.w. (weeks 0 to 4), followed by 300 mg q.4.w. (up to week 52)	180	No
				PBO q.w. (weeks 0 to 4), followed by PBO q.2.w. (weeks 4 to 16) then SEC q.2.w. or q.4.w. (up to week 52)	180	Yes

ADA = adalimumab; BKZ = bimekizumab; NMA = network meta-analysis; OLE = open-label extension; PBO = placebo; q.w. = every week; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; RCT = randomized controlled trial; SEC = secukinumab; trt = treatment.

Source: Indirect Treatment Comparison Report.⁵⁰

Table 41: Summary of Patient Characteristics for Studies Included in the NMA (N = 9)

Characteristics	HS0001	BE HEARD I	BE HEARD II	PIONEER I	PIONEER II	NCT00918255 ^a	SHARPS	SUNRISE	SUNSHINE
Intervention	BKZ vs. ADA vs. PBO	BKZ vs. PBO	BKZ vs. PBO	ADA vs. PBO	ADA vs. PBO	ADA vs. PBO	ADA vs. PBO	SEC vs. PBO	SEC vs. PBO
N	90	505	509	307	326	102	206	543	541
Age, mean (SD) years	36.7 (12.0)	36.7 (12.0)	36.6 (12.4)	37.0 (11.1)	35.5 (11.2)	36.5 (11.4)	37.6 (11.3)	36.3 (11.4)	36.1 (11.7)
BMI, mean (SD)	34.8 (8.4)	33.8 (8.2)	32.3 (8.0)	33.8 (7.8)	32.1 (7.7)	NR (NR)	32.1 (7.1)	31.8 (7.6)	32.5 (7.6)
AN count, mean (SD)	17.7 (14.8)	16.0 (17.5)	16.5 (14.6)	14.4 (13.4)	11.3 (9.7)	NR (NR)	10.8 (10.3)	13.3 (9.1)	12.8 (8.8)
Abscesses, mean (SD)	4.8 (5.1)	3.8 (6.9)	3.2 (5.3)	2.7 (3.6)	2.2 (3.0)	1.7 (NR)	2.6 (5.1)	3.3 (4.9)	2.8 (4.0)
DT count, mean (SD)	5.1 (4.9)	3.8 (4.8)	3.4 (3.7)	4.2 (4.8)	3.4 (4.7)	4.5 (NR)	3.8 (4.7)	2.7 (3.4)	2.6 (3.4)
DLQI, mean (SD)	12.6 (7.5)	12.0 (7.1)	10.8 (6.6)	16.1 (6.9)	14.5 (7.5)	15.9 (7.6)	13.2 (7.2)	14.9 (7.06)	13.8 (6.70)
HS duration, years (SD)	9.0 (8.0)	9.0 (8.3)	7.0 (7.1)	9.1 (NR) ^b	9.5 (NR) ^b	12.4 (9.8)	10.9 (9.8)	7.4 (7.4)	7.2 (7.3)
Male, %	31.0	37.0	49.3	36.2	32.2	29.4	49.0	43.6	43.8
White, %	67.8	77.8	81.5	76.2	83.7	72.5	94	76.4	79.5
Asian, %	4.4	1.6	6.7	1.3	3.1	NR	1.0 ^c	12.2	9.4
US region, %	50.0	40.8	22.2	50.5	27.3	74.5 ^c	NR	15.2	15.2
Current smokers, %	NR	43.0	48.1	56.4	65.6	57.8	68	54.0	54.0
Hurley III, %	51	49.7	38.9	47.6	46.3	29.4	48	40.5	34.0
Prior systemic biologic therapy, %	0.0 ^d	25.1	13.0	0.0 ^e	0.0 ^e	0.0 ^e	NR	23.2	23.8

ADA = adalimumab; AN = abscess and inflammatory nodule; BKZ = bimekizumab; BMI = body mass index; DLQI = Dermatology Life Quality Index; DT = draining tunnel; HS = hidradenitis suppurativa; NR = not reported; PBO = placebo; SD = standard deviation; SEC = secukinumab; TNF = tumour necrosis factor; vs. = versus.

^aUnlicensed adalimumab arm is excluded from summaries for NCT00918255.

^bMedian reported rather than mean.

^cFrom clinicaltrials.gov record.

^dPatients were eligible if they had not previously received IL-17 or TNF-alpha inhibitor.

^ePatients were eligible if they had not previously received TNF-alpha inhibitor treatment.

Source: Indirect Treatment Comparison Report.⁵⁰



Pharmacoeconomic Review



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Abbreviations

AE	adverse event
AN	abscess and inflammatory nodule
BIA	budget impact analysis
BSC	best supportive care
CDA-AMC	Canada's Drug Agency
HiSCR	Hidradenitis Suppurativa Clinical Response
HRQoL	health-related quality of life
HS	hidradenitis suppurativa
HiSCR50	Hidradenitis Suppurativa Clinical Response 50
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
NIHB	Non-Insured Health Benefits
pCPA	pan-Canadian Pharmaceutical Alliance
QALY	quality-adjusted life-year

Executive Summary

The executive summary comprises 2 tables ([Table 1](#) and [Table 2](#)) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Bimekizumab (Bimzelx), 160 mg/mL prefilled syringe or autoinjector
Indication	At the time of submission to CDA-AMC: for the treatment of moderate to severe hidradenitis suppurativa in adults
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	December 12, 2025
Reimbursement request	For the treatment of moderate to severe hidradenitis suppurativa in adults whose disease has had an inadequate response to conventional systemic therapy.
Sponsor	UCB Canada Inc.
Submission history	Previously reviewed: Yes Indication: For the treatment of active ankylosing spondylitis in adults whose disease has responded inadequately or who are intolerant to conventional therapy Recommendation date: May 16, 2024 Recommendation: Reimburse with clinical criteria and/or conditions Indication: For the treatment of active psoriatic arthritis in adults. Recommendation date: May 15, 2024 Recommendation: Reimburse with clinical criteria and/or conditions Indication: For the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy Recommendation date: March 30, 2022 Recommendation: Reimburse with clinical criteria and/or conditions

CDA-AMC = Canada's Drug Agency; NOC = Notice of Compliance.

Note: The sponsor's application was filed on a pre-NOC basis and the pharmacoeconomic submission is reflective of the information submitted at that time. The Pharmacoeconomic Review report was not revised after the NOC was received.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov
Target population	Adults with moderate to severe HS who have experienced an inadequate response to conventional systemic therapy.
Treatment	Bimekizumab
Dose regimen	320 mg every 2 weeks for 16 weeks and every 4 weeks thereafter

Component	Description
Submitted price	\$1,625 per 1 mL prefilled syringe or autoinjector \$3,250 per 2 mL prefilled syringe or autoinjector
Submitted treatment cost	\$55,250 per patient in the first year of treatment (\$42,250 per patient per year thereafter)
Comparators	• Adalimumab^a • Secukinumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (70 years)
Key data sources	Efficacy for bimekizumab informed by the BE HEARD I and BE HEARD II trials. Efficacy of adalimumab and secukinumab informed by sponsor-submitted ITCs.
Submitted results	Bimekizumab was associated with an ICER of \$298,603 per QALY gained compared to adalimumab (incremental costs = \$149,342; incremental QALYs = 0.50). Secukinumab was dominated by adalimumab.
Key limitations	• The efficacy and safety of bimekizumab compared to secukinumab and to adalimumab are uncertain owing to a lack of head-to-head trials and limitations with the sponsor's ITCs. Results of the sponsor's ITCs suggest that bimekizumab may be associated with improvements in HiSCR compared to secukinumab; however, the magnitude of improvement is uncertain. The sponsor-submitted ITCs suggest that, compared to adalimumab, there is likely no clinically meaningful difference in the efficacy of bimekizumab. The relative frequency of AEs was not assessed in the sponsor's ITCs and was based on naive comparison in economic model. • The sponsor's model does not adequately reflect the management of moderate to severe HS in clinical practice. The model structure included 5 health states based on HiSCR score. Clinical expert input indicated that the distinction between the very high response and the high response states^b is not clinically meaningful, that is, patients in these states are not likely to have different HRQoL or health care resource costs. Further, the sponsor's model does not include outcomes noted to be important to patients and clinicians, including pain and flares. • The sponsor's model included a stopping rule based on treatment response (assessed via HiSCR score) at 16 weeks for bimekizumab and secukinumab and 12 weeks for adalimumab, such that patients who did not experience at least a 50% reduction in abscesses or nodules from baseline or had an increase from baseline in abscesses and/or draining tunnels would discontinue treatment and receive BSC for the remainder of the model horizon. Clinical expert input indicated that a decision to discontinue treatment would generally not be made before at least 6 months, that the timing of response assessment would not differ according to treatment received, and that the decision to continue or discontinue treatment would not be made based on HiSCR score alone. • The modelling of subsequent therapy is not aligned with clinical practice. In practice, patients who do not experience an adequate response to treatment would trial a higher dosage of the same biologic or switch to an alternative biologic, rather than progress directly to BSC. • Health state utility values were not modelled appropriately, in that health states in the sponsor's model were assigned different utility values depending on the model time period (initial vs. maintenance period) and treatment received (biologic vs. BSC). Health states should be assigned the same utility value regardless of treatment or time period, with any additional impacts on HRQoL explicitly modelled (e.g., via disutility values for AEs). • The long-term relative effectiveness of bimekizumab is highly uncertain owing to a lack of comparative clinical data. More than 94% of the incremental QALYs associated with bimekizumab were accrued after the pivotal trials on the basis of extrapolation.

Component	Description
CDA-AMC reanalysis results	• In the CDA-AMC base case using the sponsor's 4-health state model, the stopping rule was removed, and the same utility value was adopted for each health state regardless of time period or treatment received. CDA-AMC was unable to address the remaining limitations, including uncertainty in the submitted comparative evidence. • Results of the CDA-AMC base case suggest that the ICER for bimekizumab vs. adalimumab is \$415,848 per QALY gained (incremental costs = \$192,977; incremental QALYs = 0.46). However, given that the submitted indirect evidence suggests that there may be no clinically meaningful difference between bimekizumab and adalimumab, there is insufficient evidence to justify a price premium for bimekizumab over adalimumab^a for use in the indicated population.

AE = adverse event; AN = abscess and inflammatory nodule; BSC = best supportive care; CDA-AMC = Canada's Drug Agency; HiSCR = Hidradenitis Suppurativa Clinical Response; HRQoL = health-related quality of life; HS = hidradenitis suppurativa; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life-year; QALY = quality-adjusted life-year; vs. = versus.

^aThe sponsor assumed that all patients would receive adalimumab biosimilars.

^bThe sponsor defined very high response as a 90% to 100% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline (HiSCR90) and high response as a 75% to less than 90% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline (HiSCR75).

Conclusions

Based on a review of data from the BE HEARD I and BE HEARD II trials, bimekizumab likely results in a clinically meaningful improvement in hidradenitis suppurativa (HS) inflammatory lesions when compared to placebo after 16 weeks of treatment (refer to the clinical review report). However, bimekizumab may result in little to no clinically meaningful difference in health-related quality of life (HRQoL) or improvements in pain when compared with placebo.

There are no direct head-to-head trials of bimekizumab versus secukinumab or adalimumab. As noted in the clinical review, the results of the sponsor's indirect treatment comparisons (ITCs) suggest that bimekizumab may be associated with improvements in Hidradenitis Suppurativa Clinical Response (HiSCR) compared to secukinumab; however, the magnitude of improvement is uncertain. Compared to adalimumab, the sponsor-submitted ITCs suggest that there is likely no clinically meaningful difference in efficacy of bimekizumab.

Thus, there is insufficient evidence to suggest that bimekizumab should be priced higher than adalimumab for use in the indicated population. To ensure cost-effectiveness relative to adalimumab, the total drug costs associated with bimekizumab should not exceed the total drug costs associated with the least costly form of adalimumab.

Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, clinician groups, and drug plans that participated in the CDA-AMC review process.

Joint patient group input received from the Canadian Skin Patient Alliance and from the Hidradenitis & Me Support Group was based on information collected from 19 patients with HS in Canada. Patients described how HS negatively impacts their quality of life, family life, social interactions, intimacy with partners, and ability to work. Disease manifestations as reported by patients include drainage, severe pain, and lesions

that can make it challenging to walk, find clothes, and participate in activities of daily living. Patients indicated that daily pain, which can be difficult to control, is a feature of HS, and that the pain associated with lesions in skin folds can persist for years. Patients described experience with medications (e.g., biologics, antibiotics), surgical procedures (e.g., incision, drainage), CO₂ lasers, radiotherapy, wound care practices, lifestyle modifications, and over-the-counter treatments with limited effectiveness. Goals of therapy as described by patients include management of HS symptoms, complete cure, and the ability to enjoy personal relationships. Of the 4 respondents with bimekizumab experience, most reported that it helped manage their symptoms; however, some reported discontinuing bimekizumab because of side effects.

Clinician input was received from the Atlantic Dermatology Specialist Group. The group noted that current treatment approaches include medical and surgical management, management of comorbidities, lifestyle changes, and supportive therapy. The clinician group indicated that the goals of therapy are to clear lesions, improve symptoms (e.g., pain, drainage, odour, pruritus), prevent progression to tunnels or scarring, and improve quality of life. The group noted that adalimumab and secukinumab are indicated for moderate to severe HS and that other biologics are used off-label (e.g., infliximab, ustekinumab, anakinra). The group indicated that patients with moderate to severe HS that has responded inadequately to topical therapies and systemic antibiotics would be considered candidates for bimekizumab. Input suggested that bimekizumab would likely be used as monotherapy but could be used in combination with oral antibiotics, intralesional steroids, and topical treatments for maintenance or flares. Clinicians noted that response to treatment may differ depending on disease severity, the number of previous treatments, and the extent of concomitant comorbidities. Clinicians noted that HS responds slowly to treatment and that treatment response should be evaluated later than at least 12 weeks. Clinicians indicated that at least a 25% improvement at 12 weeks is indicative that the disease respond to treatment, and that discontinuation should be considered for those with no response or worsening symptoms at 16 weeks. Finally, the clinicians noted that bimekizumab may be unrefrigerated for longer periods than secukinumab or some forms of adalimumab, which may be more convenient for patients.

Drug plan input noted that secukinumab received a recommendation for reimbursement from the Canadian Drug Expert Committee in 2024 and is under consideration for negotiation at the pan-Canadian Pharmaceutical Alliance (pCPA), and that adalimumab (branded and biosimilars) have confidential negotiated prices. The drug plans questioned whether the patients enrolled in the bimekizumab pivotal trial are representative of patients with HS in clinical practice, in that patients with more than 20 draining tunnels at baseline were excluded.

Several of these concerns were addressed in the sponsor's model:

- The sponsor's model considered the impact of treatment on patients' HRQoL.

In addition, Canada's Drug Agency (CDA-AMC) addressed some of these concerns as follows:

- CDA-AMC removed the sponsor's stopping rule, which assumed that patients who did not experience at least a 50% reduction in AN count from baseline would discontinue treatment with bimekizumab and secukinumab at 16 weeks and treatment with adalimumab at 12 weeks.

CDA-AMC was unable to address the following concerns raised from input:

- Owing to the sponsor's model structure, CDA-AMC was unable to consider the impact of some outcomes noted to be important to patients and clinicians, including pain and flares.
- Owing to a lack of evidence, CDA-AMC was unable to evaluate the cost-effectiveness of bimekizumab versus biologics other than secukinumab and adalimumab; however, the clinical experts consulted for this review indicated that other biologics are used infrequently in clinical practice.

Economic Review

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis assessing bimekizumab compared with adalimumab and secukinumab for adults with moderate to severe HS with an inadequate response to conventional systemic therapy.¹ The modelled population was aligned with the population enrolled in the BE HEARD I and BE HEARD II clinical trials and the sponsor's reimbursement request.^{2,3} The reimbursement request is narrower than the proposed Health Canada indication, which does not restrict the use of bimekizumab to those who have had an inadequate response to conventional systemic therapy.⁴ CDA-AMC approved a deviation request from the sponsor to focus on this population, as the sponsor anticipated that the Health Canada indication would be restricted to patients with disease that has inadequately responded to conventional systemic therapy.

Bimekizumab is available as a single-use prefilled syringe or autoinjector for subcutaneous injection, with a recommended dose of 320 mg every 2 weeks up to week 16 and every 4 weeks thereafter.⁴ The submitted price of bimekizumab is \$1,625.00 per 1 mL prefilled syringe or autoinjector and \$3,250.00 per 2 mL syringe or autoinjector (each 160 mg/mL). The sponsor estimated the annual per-patient cost of bimekizumab to be \$55,250 in the first year of treatment and \$42,250 annually thereafter.¹ The sponsor estimated the first-year costs to be \$25,449 per patient for adalimumab (subsequent years: \$24,506) and \$37,808 per patient for secukinumab (subsequent years: \$35,723).¹

The modelled outcomes were clinical response (assessed using HiSCR criteria), life-years, quality-adjusted life-years (QALYs), and costs. Costs were estimated from the perspective of a public health care payer in Canada over a lifetime horizon (70 years), discounted at a rate of 1.5% per annum.

Model Structure

The sponsor submitted a Markov model with 5 health states based on HiSCR criteria and death ([Figure 1](#)).¹ The health states in the sponsor's model were defined as follows:

- Very high response: 90% to 100% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline (HiSCR90)

- High response: 75% to less than 90% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline (HiSCR75)
- Response: 50% to less than 75% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline (HiSCR50)
- Partial response: 25% to less than 50% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline; or at least 25% AN count reduction, with an increase in abscesses and/or draining tunnels from baseline (HiSCR25)
- Nonresponse: Less than 25% reduction in total AN count from baseline (HiSCR < 25).

Patients entered the model in the nonresponse health state. Patients could transition to a different health state based on treatment response (i.e., HiSCR score) or remain in the nonresponse state. The sponsor assumed that patients in either the partial response or nonresponse health state at the end of the induction phase (12 or 16 weeks, depending on the treatment received) would discontinue biologic treatment. Patients in the response, high response, or very high response health states at the end of the induction period continued receiving their initial biologic treatment until death or treatment discontinuation due to loss of efficacy or an adverse event (AE). Patients who discontinued biologic treatment were assumed to receive best supportive care (BSC) until death or the end of the analysis horizon.

Model Inputs

Baseline patient characteristics in the model were aligned with those of the BE HEARD I and BE HEARD II trials (mean age = 37 years; mean weight = 97.25 kg; 57% female).^{2,3}

Transition probabilities for bimekizumab were derived from the BE HEARD I and BE HEARD II trials for the induction period (i.e., up to week 16) and from week 16 to 48.^{2,3} The sponsor assumed that the probability of moving between health states after week 48 for patients receiving bimekizumab was equal to the probability from weeks 16 to 48. The sponsor derived the efficacy of adalimumab and secukinumab from ITCs, with efficacy for up to week 48 from network meta-analyses and beyond week 48 from matching-adjusted indirect comparisons, based on data from weeks 48 to 52.⁵ The probability of treatment discontinuation in the maintenance period was assumed to be the same for all treatments, which was derived from the BE HEARD I and BE HEARD II trials (weeks 16 to 48) and was assumed to remain constant after week 48.

The sponsor incorporated age- and sex-specific mortality risk in the model, as well as an increased risk of mortality for patients with HS compared to the general population of Canada (standardized mortality ratio = 1.35).⁶

Health state utility values were derived from EQ-5D-3L data collected in the BE HEARD I and BE HEARD II trials.^{2,3} The sponsor assumed that patients receiving a biologic would have the same utility value for each health state, and that the utility values for patients who discontinued biologic therapy (i.e., receiving only BSC) would be equal to the utility values derived from the placebo group in the BE HEARD I and BE HEARD II trials. Utility values were adjusted by sex and age.⁷ Costs, but not utility decrements, were included for AEs (hidradenitis exacerbation, sweat gland infection, and cellulitis).

Costs in the economic model included those associated with drug acquisition, health care resource use, and AEs. Drug acquisition costs, including for bimekizumab, were obtained from the Ontario Drug Benefit Formulary,⁸ and the recommended dosages were based on the Health Canada–approved monograph for each treatment. For adalimumab, all patients were assumed to receive a biosimilar form. For secukinumab, the sponsor assumed that 47% of patients receive a maintenance dose of 300 mg every 2 weeks beginning at week 16, while the remainder receive 300 mg every 4 weeks. Health care resource use was derived from frequencies reported in a National Institute for Care Excellence technical appraisal, and valued using publicly available costs for Canada.⁹⁻¹² Costs of treating AEs were obtained from the Canadian Institute for Health Information.¹⁰

Summary of Sponsor's Economic Evaluation Results

The base-case analysis was run probabilistically (3,000 iterations); sensitivity analyses were conducted deterministically. The deterministic and probabilistic results were similar. The probabilistic findings are presented in the following sections. Additional results from the sponsor's submitted economic evaluation are reported in [Appendix 3](#).

Base-Case Results

In the sponsor's base case, bimekizumab was associated with an estimated cost of \$687,024 and 20.17 QALYs over a lifetime horizon ([Table 3](#)). In sequential analysis, bimekizumab was associated with an incremental cost-effectiveness ratio (ICER) of \$298,603 relative to adalimumab (incremental costs = \$149,342; incremental QALYs = 0.50). Bimekizumab had a 0% probability of being cost-effective at a willingness-to-pay threshold of \$50,000 per QALY gained.

Results were driven by bimekizumab acquisition costs and QALYs gained in the very high response state. Approximately 94% of the incremental QALYs for bimekizumab versus adalimumab were gained in the extrapolated period of the model (i.e., beyond the 48-week duration of the BE HEARD I and BE HEARD II trials).

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs (\$)	Total QALYs	Sequential ICER (\$/QALY)
Adalimumab	537,682	19.67	Reference
Bimekizumab	687,024	20.17	298,603 vs. adalimumab
Dominated treatments			
Secukinumab	590,205	19.56	Dominated by adalimumab

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.¹

Sensitivity and Scenario Analysis Results

The sponsor conducted several scenario analyses, which explored the impact of adopting alternative inputs or assumptions related to discount rates, utility decrements, the efficacy of adalimumab and secukinumab, and treatment discontinuation (i.e., stopping rules). In all scenarios, bimekizumab was associated with the

highest total costs and highest total QALYs. The scenario with the greatest impact on the cost-effectiveness of bimekizumab was that in which an alternative stopping rule was adopted. In this scenario, patients with a nonresponse (less than 25% reduction in total AN count) to treatment (at 16 weeks for bimekizumab and secukinumab and 12 weeks for adalimumab) were assumed to discontinue treatment (ICER = \$345,217, versus adalimumab).

The sponsor conducted a scenario analysis from a societal perspective, which included additional costs associated with productivity loss. In this analysis, the ICER for bimekizumab was \$226,150 per QALY gained versus adalimumab. This was lower than the sponsor's base-case analysis using a health care payer perspective.

Appraisal of the Sponsor's Economic Evaluation

CDA-AMC identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **The comparative efficacy and safety of bimekizumab are uncertain.** There is a lack of direct head-to-head evidence comparing bimekizumab to secukinumab and adalimumab. To inform efficacy in the pharmacoeconomic model (i.e., the proportion of patients in HiSCR-based health states), the sponsor used data from the BE HEARD I and BE HEARD II trials of bimekizumab. For adalimumab and secukinumab, the model was informed by data from sponsor-submitted ITCs. As noted in the clinical review, the results of the sponsor's ITCs suggest that bimekizumab may be associated with improvements in HiSCR compared to secukinumab; however, the magnitude of improvement is uncertain. The sponsor-submitted ITCs suggest that, compared to adalimumab, there is likely no clinically meaningful difference in the efficacy of bimekizumab.

In the economic model, the sponsor included costs associated with the management of serious adverse events reported to have been experienced by at least 1 patient in the BE HEARD I or II trials of bimekizumab or in the pivotal trials of adalimumab or secukinumab. The proportion of patients who experienced each AE was included via naive comparison, without adjustment or accounting for differences in patient characteristics. Owing to the direct use of clinical trial data, it is not possible to determine if any observed differences between the therapies are solely due to the treatment or, rather, due to bias or confounding factors.

- CDA-AMC was unable to address uncertainty in the clinical efficacy and safety of bimekizumab compared to adalimumab and secukinumab.
- **The model structure does not adequately reflect the management of moderate to severe HS in clinical practice.** There are several sources of uncertainty related to the model structure. First, the sponsor's Markov model included health states based on HiSCR, categorized as very high response, high response, response, partial response, and nonresponse (refer to [Figure 1](#)). Clinician input received by CDA-AMC indicated that the distinction between very high response and high response health states is not clinically meaningful, that is, patients in these health states would not be expected to have meaningfully different HRQoL or health care resource use. The inclusion of a very

high response health state is not consistent with prior models for moderate to severe HS and was not adequately justified by the sponsor.

Second, the use of the HiSCR score does not adequately capture outcomes considered important to patients and clinicians, including pain and flare reduction or prevention, as identified in input received by CDA-AMC for this review. Both pain and flares are expected to have an impact on HRQoL and health care resource use.

- In the CDA-AMC base case, the 4-state model (i.e., high response, response, partial response, and nonresponse) was adopted, using the sponsor-provided option.
- **The sponsor's analysis included a stopping rule that is unlikely to be used in clinical practice.** The sponsor's model included a stopping rule based on response to treatment (assessed via HiSCR score) at 16 weeks for bimekizumab and secukinumab and 12 weeks for adalimumab, such that patients who did not experience at least a 50% reduction in AN count from baseline at these time points would discontinue biologic treatment and receive BSC for the remainder of the model horizon. Clinician input received by CDA-AMC indicated that these time points are commonly used in clinical trials but are of limited relevance to clinical practice, where treatment response is generally assessed after at least a 6-month trial, given that HS is generally slow to respond to treatment. The clinicians indicated that they consider discontinuing treatment earlier than 6 months only if there had been no change from baseline or if the patient's disease had worsened, and that patients whose symptoms showed at least some improvement would continue treatment for at least 6 months. Clinicians indicated that the same time point would be used in clinical practice to assess response, regardless of the treatment received, and that the decision to continue or discontinue treatment is individualized and would not be based on HiSCR score alone.
 - In the CDA-AMC base case, the stopping rule was removed. The impact of adopting the sponsor-suggested stopping rules was explored in scenario analyses.
- **Subsequent therapy was not adequately modelled.** The sponsor assumed that patients who discontinued initial treatment with bimekizumab, secukinumab, or adalimumab would receive BSC until death. Clinical expert input received by CDA-AMC indicated that patients with disease that did not respond adequately to an initial trial of bimekizumab, secukinumab, or adalimumab would trial a higher dosage or an alternative biologic, including biologics noted to be used off-label in a previous limitation. As such, the assumption that all patients would receive only BSC after discontinuation of initial treatment is inconsistent with clinical practice.
 - CDA-AMC could not address this limitation.
- **Uncertainty in long-term treatment effectiveness of bimekizumab:** In the economic model, the sponsor assumed no waning of the treatment effect, thereby implying that the benefit observed for bimekizumab in the BE HEARD I and BE HEARD II trials would be maintained indefinitely throughout the lifetime horizon of the model (70 years). Clinical expert input received by CDA-AMC for this review indicated that treatment effectiveness waning has been observed with secukinumab and that waning of effectiveness of bimekizumab may also occur with time. Given that the majority

of the incremental QALYs (94%) predicted by the sponsor's model were derived on the basis of extrapolated findings rather than observed benefit, the lack of long-term data and the lack of consideration of potential waning of effectiveness introduces considerable uncertainty into the analysis. CDA-AMC notes that the long-term extension study of bimekizumab, the BE HEARD EXT study) is ongoing, with an estimated completion date of July 28, 2026.¹³ At the time of this review, evidence pertaining to the long-term comparative effectiveness of bimekizumab beyond 48 weeks was not incorporated into the sponsor's model.

- This limitation could not be addressed owing to a lack of long-term comparative clinical data. The direction and magnitude of the impact of this limitation is unknown given that the comparative rate of potential effectiveness waning with bimekizumab versus other treatments for moderate to severe HS is unknown.
- **Health state utility values were not modelled appropriately.** In the model, the sponsor incorporated different utility values for the same health state for the initial and maintenance treatment periods. For most health states, the utility value was higher in the maintenance period compared to the initial period (range: [REDACTED] and [REDACTED]). Although the sponsor derived these treatment period-specific utility values from the initial treatment period (weeks 0 to 16) and the maintenance period (weeks 16 to 48) in the BE HEARD trials, the assumption that patients would have a different utility value (i.e., HRQoL) in the same health state lacks face validity. For example, patients in the very high response health state were assigned a utility value of [REDACTED] in the initial period and [REDACTED] in the maintenance period. The implicit consequence of this in the model is that the utility value for patients in the very high response health state increases by [REDACTED] at week 17 for bimekizumab and secukinumab and at week 13 for adalimumab.

The sponsor also assumed that patients who received BSC (i.e., after discontinuation of initial biologic treatment) would have a lower utility for the same health state than patients who continued to receive biologic therapy. Clinical expert input noted that there may be quality of life decrements associated with some of the treatments included in the basket of BSC treatments (e.g., doxycycline, isotretinoin, prednisone); however, the magnitude of this impact is uncertain.

The use of treatment-specific or time period-specific utility values contradicts the CADTH recommendation that utilities should reflect the health states in the economic model;¹⁴ that is, all health states should be assigned the same utility value and any additional impacts on HRQoL (e.g., AEs during an initial treatment period or with subsequent therapy) should be explicitly modelled.

- In the CDA-AMC base case, the utility values for the maintenance period were adopted for both the initial treatment and maintenance period using sponsor-provided values.
- **Model lacked transparency:** The sponsor's submitted model included numerous IFERROR statements, which may lead to situations in which the parameter value is overwritten with an alternative value without alerting the user to the automatized overwriting. The systematic use of IFERROR statements makes thorough auditing of the sponsor's model impractical, as it remains unclear whether the model is running inappropriately by overriding errors.

- CDA-AMC was unable to address this limitation and notes that a thorough validation of the sponsor's model was not possible.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CDA-AMC (refer to [Table 4](#)).

Table 4: Key Assumptions of the Submitted Economic Evaluation

Sponsor's key assumption	CDA-AMC comment
Patients enrolled in the BE HEARD I and BE HEARD II trials are representative of patients eligible for bimekizumab based on the Health Canada indication.	Likely appropriate. As noted in the clinical review, patients with more than 20 draining tunnels at baseline were excluded from the BE HEARD I and BE HEARD II trials, whereas the proposed Health Canada indication does not restrict usage based on the number of draining tunnels. Clinical expert input indicated that, in clinical practice, patients with more than 20 draining tunnels would be considered eligible for bimekizumab but that the proportion of patients in this subgroup is likely small (~5%). The cost-effectiveness of bimekizumab in this subgroup is unknown.
Adalimumab and secukinumab are the only relevant comparators.	Uncertain. In the sponsor's base case, bimekizumab was compared to secukinumab and adalimumab, both of which are indicated for the treatment of moderate to severe HS. Clinical expert input received by CDA-AMC, as well as guidelines for practice in Canada, ¹⁵ indicated that additional biologics may be used for the treatment of moderate to severe HS, including infliximab, ustekinumab, brodalumab, risankizumab, guselkumab, and certolizumab. However, clinical experts commented that these biologics are not commonly used in clinical practice in Canada. The cost-effectiveness of bimekizumab compared to biologics other than secukinumab and adalimumab is unknown.
All patients were assumed to receive bimekizumab once every 4 weeks during the maintenance period.	Uncertain. While this assumption is aligned with the recommended dosage in the Health Canada monograph, clinician input received by CDA-AMC for this review indicated that some patients may receive bimekizumab every 2 weeks during the maintenance period. The acquisition costs of bimekizumab may therefore be underestimated. The impact of this is expected to be minor, however, as clinical experts anticipated that most patients will receive bimekizumab at 4-week intervals.
The sponsor assumed that 47% of patients would receive secukinumab once every 2 weeks during the maintenance period.	Uncertain. As noted in the product monograph, based on clinical response, every 2 week dosing for secukinumab may be used. Clinical expert input indicated that the majority of patients with moderate to severe HS would receive secukinumab every 2 weeks. The acquisition costs of secukinumab may therefore be underestimated.
All patients were assumed to receive 40 mg of adalimumab biosimilar weekly, starting 4 weeks after the initial dose.	Uncertain. Aligned with the product monograph, the sponsor assumed that all patients receive 40 mg of adalimumab weekly, starting 4 weeks after the initial dose. However, clinical expert input indicated that many patients with moderate to severe HS receive 80 mg of adalimumab weekly. The acquisition costs of adalimumab may therefore be underestimated.

CDA-AMC = Canada's Drug Agency; HS = hidradenitis suppurativa.

CDA-AMC Reanalyses of the Economic Evaluation

Base-Case Results

CDA-AMC undertook reanalyses that addressed key limitations within the submitted model, as summarized in [Table 5](#). The CDA-AMC base case was derived by making changes to model parameter values and assumptions in consultation with clinical experts. CDA-AMC was unable to address the other limitations of the model, including uncertainty in the comparative clinical evidence, uncertainty in the long-term

effectiveness of bimekizumab, and limitations related to the sponsor's modelling approach (e.g., subsequent therapy, transparency).

Table 5: CDA-AMC Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CDA-AMC value or assumption
1. Model structure	5 health states: very high response, high response, response, partial response, nonresponse	4 health states: high response, response, partial response, nonresponse
2. Stopping rule ^a	Included	Excluded
3. Health state utility values	Different utility values were adopted for the same health states in the initial and maintenance periods and based on whether a biologic or BSC was received	Utility values for each health state were assumed to be the same regardless of the time period or treatment received using sponsor-provided values
CDA-AMC base case	—	1 + 2 + 3

BSC = best supportive care; CDA-AMC = Canada's Drug Agency; HiSCR50 = Hidradenitis Suppurativa Clinical Response 50.

^aThe stopping rule modelled by the sponsor was based on response to treatment at 16 weeks for bimekizumab and secukinumab and 12 weeks for adalimumab. At these time points, the sponsor assumed that patients who did not experience treatment response would discontinue treatment and receive BSC for the remainder of the model horizon. Treatment response in the sponsor's base case was defined as at least a 50% reduction in abscess or inflammatory nodule count from baseline (HiSCR50).

CDA-AMC undertook a stepped analysis, incorporating each change proposed in [Table 5](#) to the sponsor's base case to highlight the impact of each change ([Table 6](#); disaggregated results are presented in [Table 13](#)).

Results from the CDA-AMC base case suggest that the ICER for bimekizumab versus adalimumab is \$415,848 (incremental costs = \$192,977; incremental QALYs = 0.46). Bimekizumab had a 0.7% probability of being cost-effective at a willingness-to-pay threshold of \$50,000 per QALY gained.

Results were driven by bimekizumab acquisition costs and QALYs gained in the high response state. Similar to the sponsor's analysis, approximately 95% of the incremental QALYs for bimekizumab versus adalimumab were gained in the extrapolated period of the model (i.e., beyond the 48-week duration of the BE HEARD I and BE HEARD II trials).

Table 6: Summary of the CDA-AMC Reanalysis Results

Drug	Total costs (\$)	Total QALYs	Sequential ICER (\$/QALY)
CDA-AMC base case			
Adalimumab	653,693	21.50	Reference
Bimekizumab	846,670	21.97	415,848 vs. adalimumab
Dominated treatments			
Secukinumab	793,607	21.40	Dominated

CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; vs. = versus.

Note: Probabilistic results presented.

Scenario Analysis Results

Results of price reduction analyses using the CDA-AMC base case suggest that approximately a 36% price reduction would be required for bimekizumab to be considered cost-effective at a willingness-to-pay

threshold of \$50,000 per QALY relative to adalimumab. CDA-AMC notes that a lower price reduction is required under the CDA-AMC base case, compared to the sponsor's base case, despite a higher ICER, due to a higher proportion of patients remaining on treatment over the lifetime horizon (70 years), which is an artifact of removing the stopping rule. Thus, as patients remain on treatment for longer in the CDA-AMC base case and incremental drug acquisition costs account for a larger proportion of total drug costs, a reduction in the unit cost of bimekizumab is more impactful.

Results from the price reduction analyses are contingent on the assumption that the efficacy inputs from the sponsor's ITCs are maintained and that patients who discontinue treatment do not receive another biologic therapy. Due to the limitations outlined in the Appraisal of the Sponsor's Economic Evaluation section, it is unlikely that these assumptions will hold in clinical practice.

Table 7: CDA-AMC Price Reduction Analyses

Price reduction	Unit drug cost (\$)	ICERs for bimekizumab vs. adalimumab ^a (\$/QALY)	
		Sponsor base case	CDA-AMC reanalysis
No price reduction	1,625.00	298,603	415,848
10%	1,462.50	237,723	313,923
20%	1,300.00	176,843	211,999
30%	1,137.50	115,964	110,074
40%	975.00	55,084	8,149
50%	812.50	Bimekizumab is dominant	Bimekizumab is dominant
60%	650.00	Bimekizumab is dominant	Bimekizumab is dominant
70%	487.50	Bimekizumab is dominant	Bimekizumab is dominant
80%	325.00	Bimekizumab is dominant	Bimekizumab is dominant
90%	162.50	Bimekizumab is dominant	Bimekizumab is dominant

CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; vs. = versus.

^aAll patients were assumed to receive a biosimilar form of adalimumab in the sponsor's analysis. This assumption was maintained in the CDA-AMC reanalysis.

CDA-AMC conducted a series of scenario analyses to explore the impact of implementing a stopping rule on the cost-effectiveness of bimekizumab. Results of the scenario analysis are presented in [Appendix 4, Table 14](#).

1. Patients who did not experience at least a 50% reduction in AN count from baseline at 16 weeks for bimekizumab and secukinumab or 12 weeks for adalimumab would discontinue treatment and receive BSC for the remainder of the model horizon.
2. Patients who did not experience at least a 25% reduction in AN count from baseline at 16 weeks for bimekizumab and secukinumab or 12 weeks for adalimumab would discontinue treatment and receive BSC for the remainder of the model horizon.

Results from these scenario analyses are aligned with the CDA-AMC base case in that bimekizumab is more costly and more effective than adalimumab. However, it should be acknowledged that these scenarios do

not adequately reflect clinical practice, as patients who have an inadequate response to 1 biologic treatment would try another before receiving BSC.

Issues for Consideration

- The proposed indication for bimekizumab restricts usage to adults. Clinical expert input received by CDA-AMC indicated that earlier intervention is likely to better improve outcomes and that there is a desire among clinicians for access to bimekizumab for patients aged 12 to 17 years, given that HS typically starts around puberty and has a major impact on the course of patients' lives. The cost-effectiveness of bimekizumab in patients aged younger than 18 years is unknown owing to a lack of clinical data.
- Whether the cost-effectiveness of bimekizumab differs among patients who are biologic naive or biologic experienced is uncertain. The BE HEARD 1 and BE HEARD II trials, which informed efficacy in the economic model, included both patients who were biologic naive and biologic experienced; however, cost-effectiveness among subgroups based on treatment experience was not considered in the sponsor's economic evaluation.
- Clinical expert input received by CDA-AMC, as well as guidelines for practice in Canada,¹⁵ indicated that additional biologics not included in the sponsor-submitted model (i.e., infliximab, ustekinumab, brodalumab, risankizumab, guselkumab, and certolizumab) are used in the treatment of moderate to severe HS. Clinical expert input highlighted that the frequency of use for off-label treatments varies widely by jurisdiction. The cost-effectiveness of bimekizumab versus biologics other than secukinumab and adalimumab is unknown.
- Bimekizumab and secukinumab are listed on some public formularies (e.g., for plaque psoriasis). Secukinumab is currently under consideration for negotiations with pCPA for the treatment of HS.¹⁶ Adalimumab and adalimumab biosimilars are listed on most public formularies and reimbursed for HS. It is therefore likely that bimekizumab, secukinumab, and adalimumab are reimbursed by jurisdictional drug plans at confidential prices that are lower than publicly available list prices.
- CADTH previously reviewed adalimumab and secukinumab for the treatment of moderate to severe HS in adults with disease that has not responded to conventional systemic therapy.^{17,18} The cost-effectiveness results of these evaluations may not be directly comparable to those in the current review, owing to differences in model structure, clinical effectiveness parameters, health state utility values, and cost inputs.

Overall Conclusions

Based on the clinical review of data from the BE HEARD I and BE HEARD II trials, bimekizumab likely results in a clinically meaningful improvement in HS inflammatory lesions (as measured by HiSCR50 response) when compared to placebo after 16 weeks of treatment. However, bimekizumab may result in little to no clinically meaningful difference in HRQoL or improvements in pain when compared with placebo.

There are no direct head-to-head trials of bimekizumab versus biologics indicated for the treatment of moderate to severe HS (i.e., secukinumab or adalimumab) nor trials of bimekizumab versus other biologics

that may be used off-label in clinical practice (refer to [Table 9](#)). The results of the sponsor-submitted ITCs suggest that bimekizumab may be associated with improvements in HiSCR compared to secukinumab; however, the magnitude of improvement is uncertain. The sponsor-submitted ITCs suggest that, compared to adalimumab, there is likely no clinically meaningful difference in the efficacy of bimekizumab. Indirect evidence comparing bimekizumab to any other biologic was not submitted.

The sponsor submitted an economic analysis comparing the cost-effectiveness of bimekizumab to secukinumab and adalimumab in the indicated population, with efficacy informed by the sponsor's ITCs. In addition to the uncertainty in the clinical evidence, CDA-AMC identified several additional sources of uncertainty in the sponsor's economic submission, including the use of a 5-state HiSCR-based model, the inclusion of a stopping rule for treatment discontinuation not likely to be used in clinical practice, the impact of subsequent therapy, uncertainty in the long-term effectiveness of bimekizumab, and uncertainty in the health state utility values.

CDA-AMC undertook reanalyses to address some of the limitations in the sponsor's analysis, which included adopting the sponsor-provided 4-health state model, removing the stopping rule, and adopting the same utility value for each health state, irrespective of the time period or treatment received. The results of the CDA-AMC base case are similar to the sponsor's in that bimekizumab is associated with greater costs and higher QALYs compared with adalimumab. In the CDA-AMC base case, bimekizumab was associated with an ICER of \$415,848 per QALY gained relative to adalimumab (incremental costs = \$192,977; incremental QALYs = 0.46), with a 0.7% probability of being cost-effective at a willingness-to-pay threshold of \$50,000 per QALY gained. While the CDA-AMC base case suggests that there may be a small difference in QALYs associated with bimekizumab versus adalimumab (0.46 QALYs), approximately 95% of the incremental QALYs were accrued during the extrapolation period (i.e., beyond the 48-week duration of the BE HEARD I and BE HEARD II trials). This result should also be viewed in the context of the sponsor-submitted indirect evidence, which suggests that there is likely no clinically meaningful difference in the efficacy of bimekizumab versus adalimumab. Thus, the difference in QALYs between bimekizumab and adalimumab is likely smaller than predicted in the CDA-AMC base case.

Overall, there is insufficient evidence to suggest that bimekizumab should be priced higher than adalimumab for the treatment of moderate to severe HS that has inadequately responded to conventional systemic therapy. Therefore, to ensure cost-effectiveness relative to adalimumab, the total drug costs associated with bimekizumab should not exceed the total drug costs associated with the least costly form of adalimumab.

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Appendix 1: Cost Comparison Table

Please note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s) and drug plans. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CDA-AMC Cost Comparison Table for Moderate to Severe HS

Treatment	Strength	Form	Price	Recommended dosage	Daily cost (\$)	Annual cost (\$)
Bimekizumab (Bimzelx)	160 mg/1 mL 320 mg/2 mL	Prefilled pen or autoinjector	1,625.0000 ^a 3,250.0000 ^a	320 mg every 2 weeks up to Week 16; 320 mg every 4 weeks thereafter	Year 1: 151.69 Year 2+: 116.07	Year 1: 55,366 Year 2+: 42,366
Biologics						
Adalimumab (Humira)	20 mg/0.2 mL 40 mg/0.8 mL	Prefilled pen or autoinjector	397.0500 ^b 794.1000 ^b	160 mg at Week 0; 80 mg at Week 2; 40 mg weekly thereafter starting Week 4	Year 1: 117.79 Year 2+: 113.44	Year 1: 42,995 Year 2+: 41,407
Adalimumab biosimilars	20 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL		235.6350 235.6350 471.2700 471.2700 942.5400		Year 1: 69.91 Year 2+: 67.32	Year 1: 25,516 Year 2+: 24,573
Secukinumab (Cosentyx)	150 mg/mL		934.0400		Year 1: 85.91 to 146.23 Year 2+: 66.72 to 133.43	Year 1: 31,357 to 53,374 Year 2+: 24,352 to 48,704

Note: All prices are from the Ontario Drug Benefit Formulary (accessed January 2025),¹⁹ unless otherwise indicated, and do not include dispensing fees. Recommended dosages are based on the respective product monograph. Annual period assumes 365 days.

^aSponsor-submitted price.¹

^bOntario Exceptional Access Program (accessed January 2025).²⁰

Table 9: CDA-AMC Cost Comparison Table for Moderate to Severe HS (Nonindicated)

Treatment	Strength	Form	Price	Recommended dosage	Daily cost (\$)	Annual cost (\$)
Brodalumab (Siliq)	210 mg/1.5 mL	Prefilled syringe	645.0000	210 mg weekly or every 2 weeks	23.04 to 46.07	8,408 to 16,816
Certolizumab (Cimzia)	200 mg/mL	Prefilled syringe or prefilled pen	694.4100 ^b	400 mg every 2 to 4 weeks	49.60 to 99.20	18,104 to 36,209
Guselkumab (Tremfya)	100 mg/mL	Prefilled syringe or autoinjector	3,059.7400	100 mg every 4 weeks	109.28	39,886

Treatment	Strength	Form	Price	Recommended dosage	Daily cost (\$)	Annual cost (\$)
Infliximab (Remicade)	100 mg	Vial for IV infusion	987.5600 ^b	10 mg/kg every 4 weeks	352.70	128,736
Infliximab biosimilar (Avsola, Renflexis)			493.0000		176.07	64,266
Infliximab biosimilar (Inflectra)			525.0000		187.50	68,438
Risankizumab (Skyrizi)	75 mg/0.83 mL 150 mg/mL	Prefilled syringe	2,467.5000 4,935.0000	150 mg every 4 weeks	176.25	64,331
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/mL	Prefilled syringe, autoinjector, or vial for SC injection	4,593.1400 4,593.1400	90 mg every 4 weeks	164.04	59,875
Ustekinumab biosimilar (Jamteki, Wezlana, Steqeyma)	45 mg/0.5 mL 90 mg/mL		2,755.8840 4,593.1400			

HS = hidradenitis suppurativa; SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed January 2025),¹⁹ unless otherwise indicated, and do not include dispensing fees. Recommended dosages are based on clinical expert input. A body weight of 95 kg is assumed for treatments with weight-based dosing. Annual period assumes 365 days.

Appendix 2: Submission Quality

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Table 10: Submission Quality

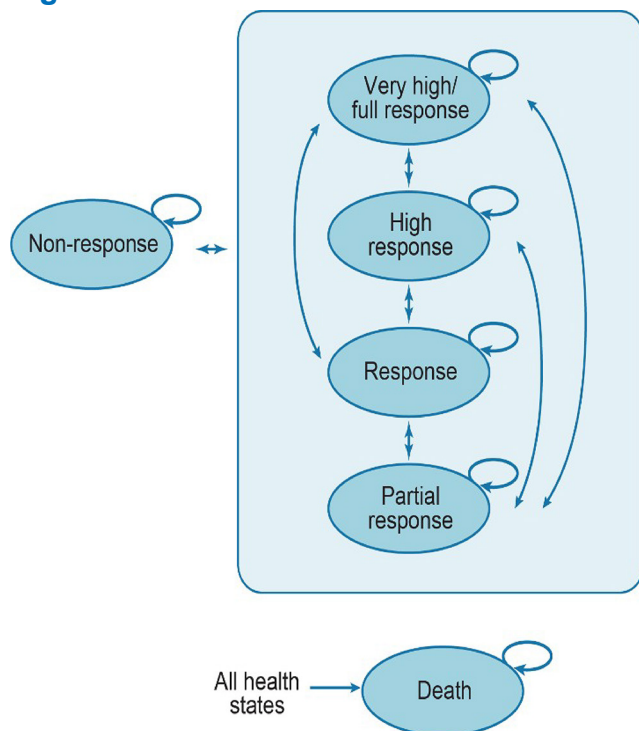
Description	Yes or no	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	No	Refer to key limitations
Model has been adequately programmed and has sufficient face validity	No	Refer to key limitations
Model structure is adequate for decision problem	No	Refer to key limitations
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	NA
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	NA
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	Yes	NA

NA = not applicable.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Please note that this appendix has not been copy-edited.

Figure 1: Model Structure



Note: Very high response was defined by the sponsor as HiSCR90 (90% to 100% reduction from baseline in total abscess and inflammatory nodule [AN] count with no increase in abscesses or draining tunnels from baseline). High response was defined as HiSCR75 (75% to less than 90% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline). Response was defined as HiSCR50 (50% to less than 75% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline). Partial response was defined as HiSCR25 (25% to less than 50% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline; or at least 25% AN count reduction, with an increase in abscesses and/or draining tunnels from baseline). Nonresponse was defined as HiSCR < 25 (less than 25% reduction in total AN count from baseline).

Source: Sponsor's pharmacoeconomic submission.¹

Detailed Results of the Sponsor's Base Case

Table 11: Disaggregated Summary of the Sponsor's Economic Evaluation Results

Parameter	Bimekizumab	Adalimumab	Secukinumab
Discounted LYs			
Total	30.85	30.85	30.85
Discounted QALYs			
Total	20.17	19.67	19.56
Nonresponse	14.85	16.50	16.82
Partial response	1.12	1.40	1.40
Response	0.74	0.53	0.54
High response	1.01	0.44	0.36
Very high response	2.45	0.82	0.44
Discounted costs (\$)			
Total	687,024	537,682	590,205
Drug acquisition	346,665	169,014	215,035
Administration	0	0	0
Resource use	339,909	368,668	374,278
Adverse events	450	0	892

HiSCR = Hidradenitis Suppurativa Clinical Response; LY = life-year; QALY = quality-adjusted life-year.

Note: Very high response was defined by the sponsor as HiSCR90 (90% to 100% reduction from baseline in total abscess and inflammatory nodule [AN] count with no increase in abscesses or draining tunnels from baseline). High response was defined as HiSCR75 (75% to less than 90% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline). Response was defined as HiSCR50 (50% to less than 75% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline). Partial response was defined as HiSCR25 (25% to less than 50% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline; or at least 25% AN count reduction, with an increase in abscesses and/or draining tunnels from baseline). Nonresponse was defined as HiSCR < 25 (less than 25% reduction in total AN count from baseline).

Source: Sponsor's pharmacoeconomic submission.¹

Appendix 4: Additional Details on the CDA-AMC Reanalyses and Sensitivity Analyses of the Economic Evaluation

Please note that this appendix has not been copy-edited.

Detailed Results of CDA-AMC Base Case

Table 12: Summary of the Stepped Analysis of the CDA-AMC Base-Case Results

Stepped analysis	Drug	Total costs (\$)	Total QALYs	Sequential ICER (\$/QALY)
Sponsor base case (probabilistic)	Adalimumab	537,682	19.67	Reference
	Secukinumab	590,205	19.56	Dominated
	Bimekizumab	687,024	20.17	298,603 vs. adalimumab
Sponsor base case	Adalimumab	542,004	20.15	Reference
	Secukinumab	589,588	20.04	Dominated
	Bimekizumab	689,922	20.67	280,568 vs. adalimumab
1. CDA-AMC reanalysis: 4-state model ^a	Adalimumab	542,149	20.15	Reference
	Secukinumab	589,561	20.04	Dominated
	Bimekizumab	690,635	20.66	289,863 vs. adalimumab
2. CDA-AMC reanalysis: remove stopping rule	Adalimumab	652,602	20.89	Reference
	Secukinumab	784,467	20.79	Dominated
	Bimekizumab	826,280	21.37	367,142 vs. adalimumab
3. CDA-AMC reanalysis: revised utilities	Adalimumab	542,004	21.68	Reference
	Secukinumab	589,588	21.61	Dominated
	Bimekizumab	689,922	22.07	374,597 vs. adalimumab
CDA-AMC base case (1 + 2 + 3)	Adalimumab	652,763	21.98	Reference
	Secukinumab	784,362	21.89	Dominated
	Bimekizumab	827,325	22.43	389,824 vs. adalimumab
CDA-AMC base case (1 + 2 + 3) (probabilistic)	Adalimumab	653,693	21.50	Reference
	Secukinumab	793,607	21.40	Dominated
	Bimekizumab	846,670	21.97	415,848 vs. adalimumab

CDA-AMC = Canada's Drug Agency; HiSCR = Hidradenitis Suppurativa Clinical Response; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Note: Results of deterministic analyses are presented unless otherwise noted.

^aIn CDA-AMC reanalysis 1, the sponsor's 4-state model was adopted. High response was defined as HiSCR75 (75% to 100% reduction from baseline in total abscess and inflammatory nodule [AN] count with no increase in abscesses or draining tunnels from baseline). Response was defined as HiSCR50 (50% to less than 75% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline). Partial response was defined as HiSCR25 (25% to less than 50% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline; or at least 25% AN count reduction, with an increase in abscesses and/or draining tunnels from baseline). Nonresponse was defined as HiSCR < 25 (less than 25% reduction in total AN count from baseline).

Table 13: Disaggregated Summary of CDA-AMC Economic Evaluation Results

Parameter	Bimekizumab	Adalimumab	Secukinumab
Discounted LYs			
Total	30.92	30.92	30.92
Discounted QALYs			
Total	21.97	21.50	21.40
Nonresponse	13.78	15.60	15.93
Partial response	1.52	2.43	2.62
Response	1.17	1.01	1.09
High response	5.49	2.46	1.76
Discounted costs (\$)			
Total	846,670	653,693	793,607
Drug acquisition	539,355	312,924	444,181
Administration	0	0	0
Resource use	306,508	340,769	347,385
Adverse events	808	0	2,041

CDA-AMC = Canada's Drug Agency; HiSCR = Hidradenitis Suppurativa Clinical Response; LY = life-year; QALY = quality-adjusted life-year.

Note: High response was defined as HiSCR75 (75% to 100% reduction from baseline in total abscess and inflammatory nodule [AN] count with no increase in abscesses or draining tunnels from baseline). Response was defined as HiSCR50 (50% to less than 75% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline). Partial response was defined as HiSCR25 (25% to less than 50% reduction from baseline in total AN count with no increase in abscesses or draining tunnels from baseline); or at least 25% AN count reduction, with an increase in abscesses and/or draining tunnels from baseline. Nonresponse was defined as HiSCR < 25 (less than 25% reduction in total AN count from baseline).

Table 14: Summary of CDA-AMC Scenario Analyses

Stepped analysis	Drug	Total costs (\$)	Total QALYs	ICER (\$/QALY)
CDA-AMC base case	Adalimumab	653,693	21.50	Reference
	Secukinumab	793,607	21.40	Dominated
	Bimekizumab	846,670	21.97	415,848
Scenario 1: Stopping rule 1 ^a	Adalimumab	537,507	21.28	Reference
	Secukinumab	588,010	21.21	Dominated
	Bimekizumab	698,010	21.67	416,824
Scenario 2: Stopping rule 2 ^b	Adalimumab	627,547	21.30	Reference
	Secukinumab	748,323	21.22	Dominated
	Bimekizumab	836,616	21.76	447,208

BSC = best supportive care; CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Probabilistic results are presented.

^aPatients who did not experience at least a 50% reduction in abscesses or nodules from baseline at 16 weeks for bimekizumab and secukinumab or 12 weeks for adalimumab would discontinue treatment and receive BSC for the remainder of the model horizon.

^bPatients who did not experience at least a 25% reduction in abscesses or nodules from baseline at 16 weeks for bimekizumab and secukinumab or 12 weeks for adalimumab would discontinue treatment and receive BSC for the remainder of the model horizon.

Appendix 5: Submitted Budget Impact Analysis and CDA-AMC Appraisal

Please note that this appendix has not been copy-edited.

Table 15: Summary of Key Take-Aways

Key take-aways of the budget impact analysis
• CDA-AMC identified the following key limitations with the sponsor's analysis: the number of eligible patients is likely underestimated, treatment costs are likely underestimated, the uptake of bimekizumab is uncertain, and the presence of confidential prices for bimekizumab and comparators. • CDA-AMC revised the sponsor's submitted analysis by aligning the estimates for the prevalence of HS and the proportion of patients eligible for public drug coverage with published literature from Canada. In the CDA-AMC base case, the budget impact of reimbursing bimekizumab for adult patients with moderate to severe HS who have had an inadequate response to conventional systemic therapy is expected to be \$137,492,877 (Year 1 = \$4,457,321; Year 2 = \$44,640,920; Year 3 = \$88,394,636). • The estimated budget impact is highly sensitive to the prevalence of HS.

CDA-AMC = Canada's Drug Agency; HS = hidradenitis suppurativa.

Summary of Sponsor's Budget Impact Analysis

In the submitted budget impact analysis (BIA), the sponsor assessed the budget impact of reimbursing bimekizumab for adult patients with moderate to severe HS who have had an inadequate response to conventional systemic therapy. The BIA was undertaken from the perspective of a publicly funded health care payer in Canada over a 3-year horizon (2026 to 2028) using an epidemiologic approach. The sponsor's estimates reflect the aggregated results from all participating jurisdictions, as well as the Non-Insured Health Benefits (NIHB) Program. The sponsor assumed that the impact of double counting of patients who are covered by both the NIHB program and provincial drug plans would be minimal. Data to inform the model were obtained from various sources, including the published literature,^{21,22} the sponsor's internal data, Statistics Canada,²³ and a draft Reimbursement Recommendation.²⁴

The sponsor compared a reference scenario in which patients received secukinumab or adalimumab to a new drug scenario in which bimekizumab was reimbursed. The uptake of bimekizumab in the new drug scenario was assumed to be approximately 13% by year 3, based on the sponsor's internal market forecasting. Bimekizumab was assumed to displace all comparators, proportionate to their respective market shares in the reference scenario. The analysis included drug acquisition costs for bimekizumab based on the sponsor's submitted price and public list prices for comparators and excluded dispensing fees and markups. The sponsor assumed that all patients who received adalimumab would receive a biosimilar form, that secukinumab would become publicly reimbursed for HS in 2025 and that 50% of patients will receive a maintenance dose of 300 mg every 2 weeks beginning at week 16. Additionally, the sponsor assumed that 10% of prevalent patients switch biologic therapy each year and incur induction treatment costs. Additional key inputs to the BIA are documented in [Table 16](#).

Table 16: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Target population	
Proportion of adults in the general population in Canada	79.0% ²³
HS prevalence	1.0% ²⁴
HS incidence	0.028% ²¹
Proportion of adult patients with moderate to severe HS	45.0% ²²
Proportion of adult patients with moderate to severe HS who are receiving biologic/advanced therapy	15.0% ^a
Proportion of patients who are eligible for public coverage	50.0% ^a
Number of patients eligible for drug under review	9,150 / 9,363 / 9,577
Market uptake (3 years)	
Uptake (reference scenario)	
Adalimumab	85.5% / 85.5% / 85.5%
Secukinumab	14.5% / 14.5% / 14.5%
Uptake (new drug scenario)	
Bimekizumab	0.5% / 6.7% / 12.7%
Adalimumab	85.0% / 81.6% / 77.8%
Secukinumab	14.5% / 11.7% / 9.5%
Cost of treatment (per patient, per year)	
Bimekizumab ^b	Year 1: \$58,500; Year 2+: \$42,250
Adalimumab ^c	Year 1: \$25,920; Year 2+: \$24,506
Secukinumab ^d	Year 1: \$42,966; Year 2+: \$36,428

HS = hidradenitis suppurativa.

^aBased on internal forecasting.

^bIn the maintenance phase, the sponsor assumed that all patients receive 320 mg every 4 weeks.

^cAll patients were assumed by the sponsor to receive a biosimilar form of adalimumab in the sponsor's analysis. In the maintenance phase, the sponsor assumed that all patients receive 40 mg weekly.

^dIn the maintenance phase, the sponsor assumed that 50% of patients receive 300 mg every 2 weeks and 50% receive 300 mg every 4 weeks.

Summary of the Sponsor's BIA Results

Results of the sponsor's analysis suggest that the 3-year budget impact of reimbursing bimekizumab for adult patients with moderate to severe HS who have had an inadequate response to conventional systemic therapy will be \$27,730,580 (Year 1 = \$896,973; Year 2 = \$9,005,319; Year 3 = \$17,828,288).

CDA-AMC Appraisal of the Sponsor's BIA

CDA-AMC identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **The number of patients eligible for bimekizumab is likely underestimated.** The sponsor used an epidemiologic approach to estimate the number of eligible patients, starting with an estimated prevalence of HS of 1%. This estimate was based on an estimated prevalence in North America and Europe.²⁴ Clinical expert input received by CDA-AMC as well as published studies suggest that the prevalence of HS in Canada is closer to 4%.²⁵ Next, the sponsor assumed that 45% of patients with HS have moderate to severe disease based on the proportion of patients with Hurley stage II or Hurley stage III HS in a retrospective single-centre chart review in Calgary, Alberta.²² Clinical expert input agreed that this estimate is reasonable; however, estimates in the literature range from approximately 57% to 85%.^{26,27} Lastly, the sponsor estimated that 50% of patients with moderate to severe HS receiving biologic or advanced therapy are eligible for public drug coverage. This is lower than the proportion of patients eligible for public drug coverage based on a 2022 report by the Conference Board of Canada (65.6% among patients aged 25 years and older).²⁸ As the estimates informing the sponsor's BIA, as described in Table 16, are lower than alternative estimates in the literature, the number of patients eligible for bimekizumab, and consequently the budget impact of reimbursing bimekizumab, is likely underestimated.
 - In the CDA-AMC base case, the prevalence of HS was assumed to be 3.84% and the proportion of patients eligible for public drug coverage was assumed to be 65.6%.
- **Drug acquisition costs are uncertain and likely underestimated:** The acquisition costs for bimekizumab, secukinumab, and adalimumab are all likely underestimated in the BIA, to varying extents. For bimekizumab, the sponsor assumed that all patients received 320 mg bimekizumab once every 4 weeks during the maintenance period. While this dosage is aligned with the Health Canada monograph,⁴ clinician input received by CDA-AMC for this review anticipates that some patients (< 10%) may receive 320 mg bimekizumab every 2 weeks during the maintenance period. For secukinumab, the sponsor assumed that 50% of patients would receive 300 mg secukinumab once every 2 weeks during the maintenance period (remainder receiving 300 mg every 4 weeks). This is higher than incorporated in the sponsor's submitted cost-utility analysis (47% assumed to receive 300 mg secukinumab once every 2 weeks during the maintenance period). However, clinical expert input received by CDA-AMC indicated that at least 75% of patients with moderate to severe HS are expected to receive secukinumab every 2 weeks in clinical practice. Lastly, for adalimumab, the sponsor assumed that all patients would receive 40 mg per week, starting 4 weeks after the initial dose, which is aligned with the Health Canada product monograph. However, clinical expert input indicated that between 70% and 80% of patients with moderate to severe HS receive 80 mg adalimumab per week.
 - CDA-AMC was unable to address this limitation. Based on clinical expert input, the underestimation of treatment acquisition costs is greater for secukinumab and adalimumab than bimekizumab, which would lead to the budget impact of reimbursing bimekizumab being overestimated. However, the dose of each drug received is expected to be dependent on patient response and may differ from the expert input.

- **The market uptake of bimekizumab is uncertain:** The sponsor estimates that 0.5%, 6.7%, and 12.7% of eligible patients will receive bimekizumab in year 1, year 2, and year 3, respectively, based on internal forecasting. Clinical expert feedback obtained by CDA-AMC suggests that the market uptake of bimekizumab may be underestimated in all 3 years, as clinicians may prefer bimekizumab over adalimumab and that bimekizumab may capture a larger market share from adalimumab in each year than anticipated by the sponsor.
 - CDA-AMC explored the impact of uncertainty in the uptake of bimekizumab in scenario analyses.
- **The prices paid by public drug plans are uncertain:** The prices for bimekizumab, secukinumab, and adalimumab were based on publicly available list prices and may not reflect the actual prices paid by public drug plans. Bimekizumab and secukinumab are listed on some public formularies (e.g., for plaque psoriasis), and secukinumab is currently under consideration for negotiations with pCPA for the treatment of HS.¹⁶ Adalimumab biosimilars are listed on some public formularies and reimbursed for HS. It is therefore likely that bimekizumab, secukinumab, and adalimumab are reimbursed by jurisdictional drug plans at confidential prices that are less than publicly available list prices.
 - CDA-AMC was unable to address this limitation.
- **The NIHB population was inappropriately calculated:** First, the sponsor calculated the total population of CDA-AMC participating drug plans by adding the population of the provinces, excluding Quebec, to the population of NIHB clients. NIHB clients living within the borders of a province are counted within provincial population data as reported by Statistics Canada, thus the NIHB population was double counted in the sponsor's analysis. Second, NIHB clients residing within Ontario who are aged < 25 years or ≥ 65 years are eligible for reimbursement by the Ontario Drug Benefit and thus should be counted as Ontario Drug Benefit clients and included in the Ontario population estimates rather than NIHB clients for the purposes of modelling the budget impact of reimbursing bimekizumab.
 - CDA-AMC did not adjust for this limitation in reanalysis. The impact on pan-Canadian model results is expected to be minimal.

CDA-AMC Reanalyses of the BIA

CDA-AMC revised the sponsor's submitted analysis by aligning the estimates for the prevalence of HS and the proportion of patients eligible for public drug coverage with published estimates from Canada. The changes made to derive the CDA-AMC base case are described in [Table 17](#).

Table 17: CDA-AMC Revisions to the Submitted BIA

Stepped analysis	Sponsor's value or assumption	CDA-AMC value or assumption
Changes to derive the CDA-AMC base case		
1. Prevalence of HS	1.00%	3.84% ²⁵
2. Proportion of patients eligible for public drug coverage	50%	65.64% ²⁸
CDA-AMC base case	Reanalysis 1 + 2	

BIA = budget impact analysis; CDA-AMC = Canada's Drug Agency; HS = hidradenitis suppurativa.

The results of the CDA-AMC step-wise reanalysis are presented in summary format in [Table 18](#) and a more detailed breakdown is presented in [Table 19](#). Results of the CDA-AMC base case suggest that the 3-year budget impact of reimbursing bimekizumab for adult patients with moderate to severe HS who have had an inadequate response to conventional systemic therapy will be \$137,492,877 (Year 1 = \$4,457,321; Year 2 = \$44,640,920; Year 3 = \$88,394,636).

Table 18: Summary of the CDA-AMC Reanalyses of the BIA

Stepped analysis	Three-year total (\$)
Submitted base case	27,730,580
CDA-AMC reanalysis 1: Prevalence of HS	104,732,539
CDA-AMC reanalysis 2: Proportion of patients who are eligible for public drug coverage	36,404,706
CDA-AMC base case	137,492,877

BIA = budget impact analysis; CDA-AMC = Canada's Drug Agency; HS = hidradenitis suppurativa.

CDA-AMC conducted the following scenario analyses to address remaining uncertainty, using the CDA-AMC base case (results are provided in [Table 19](#)):

1. Assuming higher uptake of bimekizumab in each year (5% in Year 1, 10% in Year 2, and 20% in Year 3). The additional market share for bimekizumab was assumed to be captured from adalimumab.

Table 19: Detailed Breakdown of the CDA-AMC Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation) (\$)	Year 1 (\$)	Year 2 (\$)	Year 3 (\$)	Three-year total (\$)
Submitted base case	Reference	229,132,483	242,529,697	248,178,889	253,828,082	744,536,668
	New drug	229,132,483	243,426,670	257,184,209	271,656,370	772,267,248
	Budget impact	0	896,973	9,005,319	17,828,288	27,730,580
CDA-AMC base case	Reference	1,153,561,281	1,220,754,934	1,249,189,720	1,277,624,506	3,747,569,160
	New drug	1,153,561,281	1,225,212,255	1,293,830,640	1,366,019,143	3,885,062,038
	Budget impact	0	4,457,321	44,640,920	88,394,636	137,492,877

Stepped analysis	Scenario	Year 0 (current situation) (\$)	Year 1 (\$)	Year 2 (\$)	Year 3 (\$)	Three-year total (\$)
CDA-AMC scenario 1: increased bimekizumab uptake	Reference	1,153,561,281	1,220,754,934	1,249,189,720	1,277,624,506	3,747,569,160
	New drug	1,153,561,281	1,265,328,146	1,323,934,195	1,434,127,677	4,023,390,017
	Budget impact	0	44,573,212	74,744,475	156,503,170	275,820,857

BIA = budget impact analysis; CDA-AMC = Canada's Drug Agency.



Canada's Drug Agency
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