Single Technology Appraisal

Bimekizumab for treating moderate to severe hidradenitis suppurativa [ID6134]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Bimekizumab for treating moderate to severe hidradenitis suppurativa [ID6134]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from UCB Pharma**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. British Association of Dermatologist
   b. Patient Survey

4. **Expert personal statements:**
   a. Dr Emma McMullen, Clinical expert nominated by British Association of Dermatologists
   b. Dr John Ingram, clinical expert nominated by UCB Pharma
   c. Elise Axon patient expert nominated by NICE PPIP

5. **External Assessment Report** prepared by University of York

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Bimekizumab for treating moderate to severe hidradenitis suppurativa [ID6134]

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
[ID6134] Bimekizumab HS Document B [redacted]	1.0	No	24 April 2024

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Abbreviations

A&E	accident and emergency department
ABX	antibiotics
ADA	adalimumab
AE	adverse event
ALT	alanine aminotransferase
AMS	active medication set
AN	abscess and inflammatory nodule
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BAD	British Association of Dermatologists
BDNG	British Dermatological Nursing Group
BKZ	bimekizumab
BMI	body mass index
BNF	British National Formulary
BSC	best supportive care
C-SSRS	Columbia-Suicide Severity Rating Scale
CC	clinical coding
CENTRAL	Cochrane Central Register of Controlled Trials
CfB	change from baseline
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CrI	credible interval
CSR	clinical study report
DIC	deviance information criteria
DLQI	Dermatology Life Quality Index
DT	draining tunnel
EAIR	exposure-adjusted incidence rates
EMA	European Medicines Agency
EQ-5D-3L	5-dimension, 3-level EuroQol questionnaire
ESS	effective sample size
FDA	Food and Drug Administration

FDLQI	Family Dermatology Life Quality Index
FE	fixed effects
GHQ	General Health Questionnaire
GLM	generalised logit model
HCRU	healthcare resource utilisation
HiSCR	hidradenitis suppurativa clinical response
HiSCR25	25% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining tunnel count
HiSCR50	50% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining tunnel count
HiSCR75	75% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining tunnel count
HiSCR90	90% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining tunnel count
HiSCR100	100% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining tunnel count
HiSCR-er	Hidradenitis Suppurativa Clinical Response excluding the surgical site
HiSQOL	hidradenitis suppurativa quality of life
HRG	healthcare resource group
HRQoL	health-related quality of life
HS	hidradenitis suppurativa
HSSA	Hidradenitis Suppurativa symptoms assessment
HSSDD	Hidradenitis Suppurativa Symptom Daily Diary
HSSQ	HS symptom questionnaire
IBD	inflammatory bowel disease
ICE	intercurrent event
IgG1	immunoglobulin G1
IHS4	International Hidradenitis Suppurativa Severity Score System
IHS4-55	55% reduction in IHS4 total score
IL	interleukin
IMP	investigational medical product
IQR	interquartile range
ISI	Insomnia Severity Index
MACE	major adverse cardiac events

MAIC	matching-adjusted indirect comparison
MCID	minimal clinically important difference
MCMC	Markov chain Monte Carlo imputation
MCS	Mental Component Summary
MD	Mean difference
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mNRI	modified non-responder imputation
MS	maintenance set
NC	not calculable
NMA	network meta-analysis
NR	not reported
NRI	non-responder imputation
NRS	numerical rating scale
NRS30	≥ 30% reduction and reduction of ≥ 2 units from baseline in HSSDD weekly worst skin pain NRS score, assessed in patients with a baseline NRS score of ≥ 3
OC	observed case
OHE	Office of Health Economics
OLE	open-label extension
OR	odds ratio
PCDS	Primary Care Dermatology Society
PCS	Physical Component Summary
PGA	Patient Global Assessment
PGI-C-SP	Patient Global Impression of Change in Severity of Skin Pain
PGI-S-SP	Patient Global Impression of Severity of Skin Pain
PHQ-9	Patient Health Questionnaire-9
PICOS	population, intervention, comparator, outcomes, and study design
PSS	personal social services
PRDA	Patient-rated disease activity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	patient-reported outcome
PY	patient-year
PYE	patient-years of exposure

QALY	quality-adjusted life year
QW	every week
Q2W	every 2 weeks
Q4W	every 4 weeks
RCT	randomised controlled trial
RS	randomised set
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SE	standard error
SF-12	12-item short form health survey
SF-36	36-item short form health survey
SIB	suicidal ideation and behaviour
SLR	systematic literature review
SmPC	summary of product characteristics
SMQ	standardised MedDRA queries
SS	Safety Set
STA	Single Technology Appraisal
SUCRA	surface under the cumulative ranking curve
TEAE	treatment-emergent adverse event
Th17	T helper 17
TSU	technical support document.
ULN	upper limit of normal
VAS	visual analogue scale

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation: adults with active moderate to severe hidradenitis suppurativa (HS) who have an inadequate response to conventional systemic treatments and for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment. The proposed position in the treatment pathway is narrower than the marketing authorisation because this position optimises the cost effectiveness of bimekizumab; bimekizumab is not anticipated to be cost effective versus adalimumab due to the availability of adalimumab biosimilars.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with moderate to severe HS	Adults with active moderate to severe HS who have an inadequate response to conventional systemic treatments and for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment	This position optimises the cost effectiveness of bimekizumab
Intervention	Bimekizumab	Bimekizumab Q2W to week 16, followed by bimekizumab Q4W	
Comparator(s)	• Adalimumab • Secukinumab (where adalimumab is not suitable, did not work or has stopped working) • Best supportive care	• Secukinumab • Best supportive care (including some adalimumab use due to limited treatment options; assumed to be used by 20.8% of patients on BSC in the cost-effectiveness model)	Bimekizumab is anticipated to be positioned in the UK for people with moderate to severe HS for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment. Therefore, adalimumab is not a directly relevant comparator

Outcomes	• Disease severity • Disease progression • Clinical response • Inflammation and fibrosis • Discomfort and pain • Adverse effects of treatment • Health-related quality of life	• Disease progression, clinical response, and discomfort and pain, assessed as HiSCR25, **HiSCR50**,[a] HiSCR75, HiSCR90 and HiSCR100 responses, HS lesion counts, IHS4, IHS4-55 responses, flare, the HSSDD and the HSSQ • Adverse effects of treatment, including TEAEs of interest • Health-related quality of life, assessed with the DLQI, HiSQOL and EQ-5D-3L	

[a] The proportion of patients achieving HiSCR50, defined as a 50% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining tunnel count, at week 16 was the primary endpoint of the BE HEARD trials [1, 2].

AN, abscess and inflammatory nodule; DLQI, Dermatology Life Quality Index; EQ-5D-3L, 3-level, 5-dimension EuroQol questionnaire; HiSCR, hidradenitis suppurativa clinical response; HiSQOL, Hidradenitis Suppurativa Quality of Life; HS, hidradenitis suppurativa; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary; HSSQ, HS symptom questionnaire; IHS4, International Hidradenitis Suppurativa Severity Score System; Q2W, every 2 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event.

B.1.2 Description of the technology being evaluated

A description of the technology being evaluated, bimekizumab, is shown in Table 2.

Table 2 Technology being evaluated

UK approved name and brand name	Bimekizumab (Bimzelx®)
Mechanism of action	Bimekizumab is a humanised IgG1/κ monoclonal antibody that selectively binds with high affinity to IL-17A and IL-17F homodimers and IL-17A/F cytokine heterodimers, blocking their interaction with the IL-17RA/IL-17RC receptor complex [3, 4].
Marketing authorisation/CE mark status	Marketing authorisation was granted by the European Medicines Agency (EMA) in April 2024. It is anticipated that marketing authorisation will be granted by the Medicines and Healthcare products Regulatory Agency (MHRA) in [redacted] Bimekizumab received Promising Innovative Medicine status from the MHRA in Q2 2023 for the treatment of adults with hidradenitis suppurativa (HS).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Bimzelx is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Contraindications** Hypersensitivity to the active substance or to any of the excipients listed below [3]: • Glycine • Sodium acetate trihydrate • Glacial acetic acid • Polysorbate 80 • Water for injections Clinically important, active infection, e.g., active tuberculosis **Special warning and precautions for use** These are listed in section 4.4 of the European Medicines Agency (EMA) SmPC [3]. Of note, • Bimekizumab may increase the risk of infections such as upper respiratory tract infections and oral candidiasis. • Cases of new or exacerbations of inflammatory bowel disease have been reported with bimekizumab. Bimekizumab is not recommended in patients with inflammatory bowel disease.
Method of administration and dosage	The recommended dose for adult patients with hidradenitis suppurativa is 320 mg (given as 2

	subcutaneous injections of 160mg each) every 2 weeks up to Week 16 and every 4 weeks thereafter.
Additional tests or investigations	No additional tests or investigations are needed compared with current clinical practice
List price and average cost of a course of treatment	The list price of bimekizumab is £2,443 per 320 mg dose (2 × 160 mg prefilled syringes). Assuming that patients receive 320 mg Q4W for one year, the annual cost of a bimekizumab treatment course is £31,759 at the maintenance dose (i.e., excluding the loading dose cost).
Patient access scheme (if applicable)	UCB has an existing commercial arrangement for bimekizumab. This makes bimekizumab available to the NHS with a simple confidential discount. The bimekizumab PAS discounted price is [redacted] which consists of two 160 mg prefilled syringes.

IgG1, immunoglobulin G1; IL, interleukin.

B.1.3 Health condition and position of the technology in the treatment pathway

Summary

Overview of hidradenitis suppurativa

- Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent, physically and emotionally debilitating skin disease of the hair follicle that has a profoundly negative impact on patients' mental health, daily lives and overall quality of life [5].
- HS is characterised by recurrent boil-like lumps or nodules in certain areas of the body (mostly in skin folds, often in intimate areas [5-8]) that become inflamed and painful, and can lead to abscesses, tunnels – some of which will become draining tunnels (DTs), irreversible skin damage and scarring [5-7, 9, 10].

Classification

- The severity of HS is based on the number of abscesses and inflammatory nodules, how widespread they are, and the presence of tunnels and scarring [11]. The Hurley scale for HS severity, which was originally developed for surgical purposes, is commonly used in clinical settings for defining disease severity [12-14].
- In clinical trials, treatment response is often measured as Hidradenitis Suppurativa Clinical Response (HiSCR50) a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess or DT count relative to baseline [15].
- With the development of new biological therapies, more stringent HiSCR response thresholds, reflecting 75%, 90% and 100% reductions in AN count (with no increase in abscess or DT count), are increasingly being used in clinical trials.
- HiSCR50 does not include dynamic measurement of DTs [16]; an alternative measure, the International Hidradenitis Suppurativa Severity Score System (IHS4), which includes all lesion types, is becoming more widely used [16, 17]. A dichotomous version, IHS4-55 (defined as a 55% reduction in total score), has also been validated [16, 18, 19].

Diagnostic delay

- Delays in diagnosis of HS are a significant issue, with a mean time from symptom onset to diagnosis of 10 years, during which many patients have progressed to moderate or severe disease [20-23].
- In a UK patient survey, 92% of respondents (n = 59) reported receiving at least one misdiagnosis prior to being diagnosed with HS [24].

Aetiology

- HS has a complex molecular pathology and a heterogeneous inflammatory profile. Several inflammatory pathways, particularly the interleukin (IL)-17 and tumour necrosis factor (TNF)-α pro-inflammatory cytokines, are highly active in HS [25-27].

Epidemiology

- HS affects around 0.8% of the UK population, corresponding to approximately 435,000 people in England [28].
- Despite treatment, around 45% of people with HS have moderate to severe disease (defined as Hurley stage II-III) [8]. At the time of diagnosis, the proportion of people with moderate to severe disease (based on retrospective judgement by physicians) is about 74%.

Impact on health and health-related quality of life

- The symptoms of HS include pain, itching, irreversible skin damage, fatigue, infection and foul-smelling secretions. These have a negative impact on patients' self-esteem,

sexual function, mental health, access to education, and ability to access, function and progress in the workplace [20, 29-33].
- Additional medical conditions are common among patients with HS, with over 80% having at least one comorbidity [20, 34-37].
- Impairment of health-related quality of life (HRQoL) in HS is worse than that seen in other skin diseases such as psoriasis, and is similar to or worse than that observed in patients with rheumatoid arthritis pain, chronic obstructive pulmonary disease, cancer and cardiovascular disease [38].

Impact on the NHS, society and employment

- A 2023 Office of Health Economics (OHE) report has estimated that the UK societal cost of HS, including productivity losses, out-of-pocket expenses and healthcare costs, is £19,923 per person with HS per year – this corresponds to an estimated aggregate cost in the UK of £3.8 billion [21].

Bimekizumab mechanism of action

- T helper 17 (Th17) cells are strongly implicated in established self-sustaining clinical disease, via a feedback loop mediated by interleukin (IL)-17A and IL-17F [25, 26].
- Unlike other IL-17 biologics such as secukinumab and ixekizumab that inhibit the biological function of IL-17A homodimers and IL-17A/F heterodimers, bimekizumab is a humanised immunoglobulin G1 (IgG1)/κ monoclonal antibody that selectively binds with high affinity to IL-17A and IL-17F homodimers and IL-17A/F heterodimers, blocking their interaction with the IL-17RA/IL-17RC receptor [39].
- In human cells, inhibiting both IL-17A and IL-17F with bimekizumab has been shown to suppress inflammatory gene expression and neutrophil migration to a greater degree than blockade of IL-17A alone [40]. By inhibiting both of these key pro-inflammatory cytokines, bimekizumab disrupts the Th17 cell feedback loop, reducing inflammation and improving disease symptoms [41].

Clinical pathway of care

- For patients with moderate to severe HS which has responded inadequately to conventional systemic treatment, targeted therapy with the TNF inhibitor (TNFi) adalimumab is recommended according to NICE and British Association of Dermatologists guidelines [42, 43].
- TA935 recommends secukinumab as an option for treating active moderate to severe HS in adults whose disease has not responded well enough to conventional systemic treatment, only if adalimumab is not suitable, did not work or has stopped working [44].
- For both adalimumab and secukinumab, approximately half of patients do not have a clinical response to initial treatment, and for some patients treatment works at first and then stops working (secondary failure) [44-48].
- Accordingly, for patients with moderate to severe HS there remains a need for additional well-tolerated, efficacious therapies.

Proposed positioning of bimekizumab

- The proposed positioning of bimekizumab is for adult patients with moderate to severe HS who have an inadequate response to conventional systemic treatments and for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment. This positioning would place bimekizumab alongside secukinumab in the treatment pathway.

B.1.3.1 Disease overview

B.1.3.1.1 Clinical features

HS is a chronic, inflammatory, recurrent, physically and emotionally debilitating skin disease of the hair follicle that has a profoundly negative impact on patients' mental health, daily lives and overall quality of life [5]. One respondent to a UCB survey of patients with HS in the UK conducted in March 2024 stated [24] :

"*… try and think about what it doesn't affect, and I can't think of anything it doesn't affect. It affects my* ***mobility***, ***mental health***, ***self-esteem***, ***self-worth***, *the* ***clothing I wear***, *my* ***social plans***, *my* ***sex life***, *my broader* ***relationships*** *as a* ***daughter***, *a* ***sister***, *a* ***friend*** *or* ***colleague***, *my* ***ability to start a family***, *the* ***chance to reach the level I wanted to in my career***, ***physical activity***, *my* ***employment*** *through being absent or not as productive, it has costs attached in terms of time off work for* ***sickness***, ***surgery***, ***appointments***, ***travel*** *and* ***parking costs***, ***buying OTC pain relief***, ***dressings***, ***additional clothes***, ***laundry***.."

HS is characterised by recurrent boil-like lumps or nodules in certain areas of the body (mostly in skin folds, often in intimate areas [5-8]) that become inflamed and painful, and can lead to abscesses, tunnels (also known as sinus tracts or fistulas), irreversible skin damage, scarring and decreased mobility [5-7, 9, 10]. Some tunnels can become DTs which can lead to significant pain and chronic, malodorous discharge [7, 49].

The most common areas of the body affected by HS include armpits, groin, buttocks, genitals/pubic region, breast/chest, inner thighs, anus/perianal skin, nape of neck, back and abdomen [8].

The symptoms of HS include pain/discomfort, pain on sitting, itch, skin damage, infection, foul-smelling secretions and restricted/painful movement of arms and legs [7, 8]. HS can persist for many years and worsen over time [50]. In addition, patients experience recurrent disease flares which result in worsening of symptoms including pain, leading to reduced health-related quality of life (HRQoL) [51, 52]. Patients with HS experience low self-esteem, feelings of shame, damage to social functioning and relationships, fatigue, inability to carry out daily activities or exercise, sexual dysfunction, sleep problems and deteriorations in mental health, including high rates of anxiety and depression [8, 20, 29, 31, 37, 53].

B.1.3.1.2 Diagnosis and classification

HS diagnosis

Disease characteristics based on lesion type, location and frequency are used to diagnose HS [54, 55].

Diagnostic delay and misdiagnosis are significant issues for patients with HS, with a mean time from symptom onset to diagnosis of 10 years [20-22]. In the UCB UK patient survey (n = 59), 92% of respondents reported receiving at least one misdiagnosis prior to being diagnosed with HS [24]. HS is frequently misdiagnosed as abscesses, boils and ingrown hairs, which can lead to inappropriate treatment [21]. The longer the delay until diagnosis,

the greater the disease severity at diagnosis. In a recent survey conducted in the USA, France, Germany, Italy, Spain and the UK, 74% of patients with HS already had moderate or severe disease (as judged by physicians) at the time of diagnosis, and 47% already had scarring [8]. In a Dutch study, patients with moderate and severe HS (Hurley stage II and III; see below) had reached this disease stage in a median of 6 and 5 years, respectively, following disease onset [23]. Notably, this period is shorter than the mean time to diagnosis.

There is evidence that diagnostic delays can lead to poor health outcomes [21, 56]. In particular, there is a 'window of opportunity' early in the disease course, with medical treatment most likely to be effective if started in a disease stage characterised by reversible features such as inflammatory nodules, abscesses and dermal or dermoepidermal tunnels, rather than after the development of irreversible features such as complex or subcutaneous DTs and scarring [56, 57]. In addition, as time passes biofilm formation in DTs and altered skin microbiota can make antibiotic therapy more difficult [58].

Classification of HS severity

The severity of HS is based on the number of lesions, how widespread they are, and the presence of tunnels and scarring, which are indicative of more severe disease [11]. Tunnels require time-consuming wound care, and leaks and odour can cause patients high levels of anxiety and shame; issues around dressings can lead to patients avoiding going out in public for long periods of time, impacting their ability to work, exercise and contribute to society [59]. The scarring present in more severe disease stages can only be addressed by surgery.

The Hurley scale for HS severity is commonly used in clinical and clinical trial settings for defining disease severity. The Hurley scale was originally developed for surgical purposes and is a 3-stage classification system of disease severity (Table 3 and Figure) [12-14].

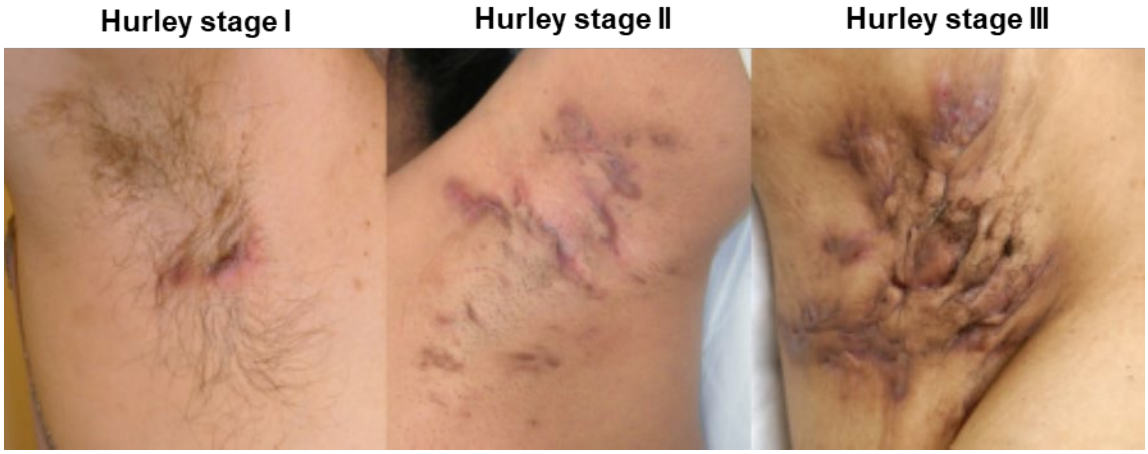
Table 3 Hurley staging system for HS

Hurley stage	Clinical features
I	Single or multiple abscesses No tunnels or scarring
II	Recurrent single or multiple widely separated abscesses Tunnels and scar formation
III	Diffuse involvement OR multiple interconnecting abscesses and tunnels

HS, hidradenitis suppurativa.

Sources: Griffin *et al.* 2017 and Hurley 1989 [5, 13, 14, 55].

Figure 1 Examples of HS at Hurley stage I, II and III



Source: Ovadja *et al.* 2019 [11].

Measurement of treatment response with HiSCR50 and related measures

In clinical trials, treatment response is typically measured with the Hidradenitis Suppurativa Clinical Response 50 (HiSCR50) and related endpoints [15]. HiSCR50 is defined as the proportion of patients with at least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess or DT count relative to baseline [15]. HiSCR50 is the primary endpoint of the BE HEARD trials described in section B.2. The term "HiSCR" is sometimes used in the clinical literature to refer to HiSCR50 specifically. In this document, the term HiSCR is instead used more broadly to refer to all HiSCR-related endpoints (e.g. HiSCR25, HiSCR50 etc.).

In clinical practice, a lower threshold (25% reduction in AN count with no increase in abscess or DT count; HiSCR25) is often used, according to advice received from UK clinicians at an HS advisory board. HiSCR25 is the definition of treatment response used in NICE TA392 [42], and in clinical practice patients are commonly remaining on treatment with adalimumab with this level of response or less, because there are insufficient alternative, more effective treatment options, leading to a high HRQoL burden and a high level of NHS resource use.

By contrast, with the development of new biological therapies, a series of additional clinical response thresholds based on the same measures are gaining in popularity, reflecting 75%, 90% and 100% reductions in AN count with no increase in abscess or DT count (HiSCR75, HiSCR90 and HiSCR100, respectively; see section B.2.3.1.6). As therapies for HS become more effective, these higher thresholds are likely to become important. Patients with a clinical response based on HiSCR50 may not have sufficient resolution of their symptoms, as a 50% improvement can still represent a substantial disease burden, with even one painful lesion being difficult for patients to live with. Accordingly, achieving a greater depth of response, measured with higher thresholds, is an important goal for patients with HS [48, 60].

The increasingly stringent thresholds gaining popularity in HS are analogous to the evolution of the psoriasis treatment landscape as more advanced biological therapies have been developed. When etanercept was approved in 2004, a 50% reduction in Psoriasis Area and

Severity Index (PASI 50) was considered to be a clinically significant endpoint in the assessment of psoriasis [61]. By 2015, a 75% reduction in PASI (PASI 75) was the therapeutic benchmark [61], and with subsequent generations of biologics 90% and 100% reductions in PASI (PASI 90 and PASI 100) have in turn been used as the primary endpoints of RCTs [62, 63].

Increasingly, therefore, higher HiSCR thresholds are likely to be used both in clinical practice and in trials of HS therapies. In the BE HEARD trials described in section B.2, HiSCR75 was a key ranked secondary endpoint – this is the first time that HiSCR75 has been used as a key ranked secondary endpoint in a pivotal, phase 3 trial. The first HS RCT (a phase 2 study of sonelokimab) to use HiSCR75 as a primary endpoint has recently been completed [64].

A limitation of HiSCR50 and related HiSCR measures of increasing stringency is the lack of dynamic measurement of DTs or symptoms such as pain, meaning that the effect of anti-inflammatory treatment may not be fully captured [16]. In principle, patients could achieve HiSCR100 but still have active DTs [65] which can cause significant pain and chronic, malodorous discharge as described above [7, 49]. A further limitation of HiSCR measures is that, being based on percentages, they cannot distinguish between large improvements for patients with severe disease and smaller improvements for those with moderate disease.

Measurement of disease severity with IHS4

To address some of the limitations of HiSCR50 and related measures, the International Hidradenitis Suppurativa Severity Score System (IHS4), which includes all lesion types, has been developed [17].

The IHS4 generates a continuous score by assigning weights to different lesion types: inflammatory nodules (1 point), abscesses (2 points) and DTs (4 points) [16, 17]. IHS4 total scores can be used to classify disease severity (≤ 3 points, mild; 4–10 points, moderate; ≥ 11 points, severe) [16, 17]. The main advantage of the IHS4 is that DTs can be taken into account as well as abscess and inflammatory nodules. A dichotomous version of the IHS4 has been developed, with a 55% reduction in total score being found to be optimal for discriminating between adalimumab- and placebo-treated patients [16, 18].

Other clinical outcome measures for HS are described in Table 9 in section B.2.3.1.6.

B.1.3.1.3 Epidemiology

A Clinical Practice Research Datalink (CPRD) Study found that in 2013 HS affected around 0.77% of the UK population, although almost one-third of cases were based on stringent questionnaire criteria rather than a physician diagnosis [28]. Using this 0.8% estimate, this corresponds to approximately 435,000 people with HS in England [28]. The mean annual incidence in the UK of physician-diagnosed HS was 29.4 per 100,000 person-years in 2013 [28].

Real-world data suggest that 45.3% of people with HS have moderate to severe disease, defined as Hurley stage II or III, despite treatment (at a mean of 41.6 months post-diagnosis)

[8]. At the time of diagnosis, the proportion with moderate to severe disease (based on retrospective judgement by physicians) is about 74% (see section B.1.3.1.2).

The onset of HS is considered to occur during puberty, with the disease typically diagnosed in young adults (aged 20–40 years) [66-68]. In European populations, HS has an incidence approximately 3 times higher in women than in men [5, 28, 66, 69]. HS is more common among people with an African–Caribbean background than among people with a European background, and reported prevalence varies greatly across the world [70].

Risk factors for HS include cigarette smoking, obesity, hormonal factors, genetic factors (there is a family history in 30% of cases) and stress [29, 70-72].

B.1.3.1.4 Impact on health and health-related quality of life

The symptoms of HS can impose a substantial burden on patients' lives and HRQoL [9].

Impact of HS on mortality

An increased risk of mortality among patients with HS has been reported in two Nordic studies and a Korean study. A Danish retrospective study found an incidence rate ratio for all-cause mortality of 1.35 (95% confidence interval [CI], 1.15–1.59) for patients with HS, compared with the general population, as well as an increased risk of myocardial infarction, stroke, cardiovascular-associated death and major adverse cardiovascular events [73]. In a Finnish study, patients with HS had an increased risk of all-cause mortality, and of death due to neoplasms or diseases of the circulatory system, compared with patients with psoriasis [74]. A retrospective population-based cohort study from Korea reported an increased risk of all-cause mortality for patients with HS (disease severity not reported) compared to controls (crude hazard ration [HR],1.15; 95% CI, 1.05–1.26) [75]. Hazards were more comparable after adjusting for body mass index, smoking, drinking and comorbidity. However, this study also reported increased all-cause mortality for patients with HS who underwent surgical procedures (crude HR, 1.86; 95% CI, 1.41–2.46; adjusted HR, 1.48; 95% CI, 1.12–1.96), suggesting that all-cause mortality is increased in this more severe subpopulation [75].

Burden of HS symptoms

Patients with HS experience pain, itching, oozing, malodour, fatigue, low self-esteem, feelings of shame, damage to social functioning and relationships, inability to carry out daily activities, sexual dysfunction, and deteriorations in mental health [8, 20, 29, 31, 53].

A questionnaire-based study of dermatologists (n = 312; 50 from the UK) and their patients (n = 1787; patient- or carer-reported data were reported for 591 patients) across five European countries (France, Germany, Italy, Spain and the UK; EU5) and the USA reported that the most common symptoms of HS were pain, inflammation, itching and drainage (Table 4) [8]. All HS symptoms increased in frequency with increasing disease severity (Table 4) [8].

Table 4 Prevalence of HS symptoms among patients in five European countries (France, Germany, Italy, Spain and the UK) and the USA

Symptom, n (%)	Overall (N = 1787)	Mild HS (N = 1179)	Moderate HS (N = 523)	Severe HS (N = 85)
General pain/discomfort	885 (49.5)	452 (38.3)	364 (69.6)	69 (81.2)
Inflammation/redness of HS lesions/abscesses	823 (46.1)	411 (34.9)	342 (65.4)	70 (82.4)
Itching	535 (29.9)	333 (28.2)	183 (35.0)	19 (22.4)
Drainage from HS lesions/abscesses	474 (26.5)	175 (14.8)	233 (44.6)	66 (77.6)
Pain on sitting	428 (24.0)	179 (15.2)	191 (36.5)	58 (68.2)
Restricted/painful movement of arms/legs	421 (23.6)	184 (15.6)	194 (37.1)	43 (50.6)
Infection of HS lesions/abscesses	295 (16.5)	121 (10.3)	141 (27.0)	33 (38.8)
Malodorous drainage	278 (15.6)	98 (8.3)	129 (24.7)	51 (60.0)
Low mood/depression	260 (14.5)	116 (9.8)	104 (19.9)	40 (47.1)
Fatigue	228 (12.8)	92 (7.8)	110 (21.0)	26 (30.6)

Symptom prevalence and disease severity were reported by responding physicians according to their judgement, with no clinical definition applied.

HS, hidradenitis suppurativa.

Source: Ingram *et al.* 2022 [8].

Pain is the predominant symptom for patients with HS but is inadequately captured by common tools for quantifying HS severity. In the Global Survey Of Impact and Healthcare Needs (VOICE), a prospective, questionnaire-based study which was conducted in 27 institutions (mostly HS referral centres) across 14 countries and included 1299 patients (719 from Europe, 493 from North America and 87 from other regions [Asia, Australia, Africa and South America]), recent HS-related pain was rated by patients on a numerical scale from 0 (no pain) to 10 (worst possible pain) [20]. Most participants (61.4%, 798/1299) rated the pain as moderate or higher (≥ 5), and 4.5% described the pain as being the worst possible (10) [20].

In a UCB survey of patients with HS in the UK conducted in March 2024 (n = 59), 80% of patients reported experiencing pain in the last 6 months and 98% of patients identified pain as the top symptom that they most wish would disappear [24]. One patient stated that [24]:

"*It is **difficult for others to truly understand the pain** and the limitations caused by HS, in part because people can't see it. Sometimes what doesn't look like much is **10 out of 10 in pain**, and other times, something which can look terrible, can be far less painful."*

Symptoms such as pain (neuropathic and nociceptive) and itch may interfere with daily function and quality and amount of sleep, thereby resulting in a less productive life and dysfunction during daytime [29]. In the UCB UK patient survey, respondents stated that HS affected their clothing choices (59%), ability to move around comfortably (43%), ability to exercise or stay active (42%) and their ability to look after themselves (30%) [24].

In a study of 108 patients with HS in Poland, itch and pain both had a significant impact of the frequency of insomnia, and pain was also associated with poor sleep quality (measured using the Pittsburgh Sleep Quality Index), with significant effects on subjective sleep quality, sleep duration and daytime dysfunction [30]. In the Global VOICE study, 61% of patients with HS reported having symptoms related to fatigue over the past week [20].

A survey of 421 patients with HS in Denmark found significant associations between loss of utility (assessed using the 5-dimension, 3-level EuroQol questionnaire [EQ-5D-3L]) and pain, malodour and itch [76].

Malodorous drainage from DTs and abscesses has a substantial impact on patients with HS. In the UCB UK patient survey, 90% of respondents wished that odour and leakage would disappear, and one patient stated that [24]:

"*Drainage, odour and dressings/wound care has a **huge physical impact**…worrying about strikethrough on your clothes being a big one.*"

In the Global VOICE study, the majority of patients with HS reported having symptoms related to drainage (72%) and odour (54%) over the past week [20]. In addition, more than 80% of patients with HS reported experiencing disease flares at least monthly [20]. DTs and abscesses require time-consuming wound care, and issues around dressings can lead to patients avoiding going out in public for long periods of time, impacting on their ability to work, access education, exercise and contribute to society [59]. Further details of the burden of wound care are described in a later paragraph within this section.

Impact of HS on patients' intimacy and sexual relationships

Another key aspect of quality of life is sexual health, which is severely affected in patients with HS [29]. In the UCB UK patient survey, 69% of people reported regularly or constantly having concerns about being intimate with a partner, and 53% reported regularly or constantly experiencing a low sex drive [24]. Further, 90% of patients surveyed reported that if their symptoms were controlled, this would positively impact their ability to be intimate with a partner [24]. One respondent stated [24]:

"*HS made me feel I would be **unable to be in a relationship** and have children"*

In the UK, a focus group study conducted by the Office of Health Economics (OHE) found that the impact of HS on self-worth and confidence when seeking a romantic partner was particularly high among young people [21]. Additionally, nearly all women (94.3%) and most men (80.8%) surveyed said HS negatively influenced their chances of having a relationship or sexual relations. Women with HS are often of childbearing age, which could significantly affect their plans for starting a family. In the UCB patient survey, 66% of patients reported HS having a considerable to devastating impact on their willingness to start a family [77].

Scores on the Female Sexual Function Index, the Index of Erectile Function and the Arizona Sexual Experience Scale indicated impaired sexual function in an analysis of 300 survey respondents with HS in the Netherlands [78]. Female sex and late onset of HS were associated with poor sexual function [78].

Impact of HS on patients' mental health

HS has a significant impact on mental health, thereby negatively affecting the quality of life of patients with HS [29].

In the UCB UK patient survey, patients reported constantly or regularly experiencing: reduced self-esteem and confidence (69%); feeling depressed (54%); feeling stigmatized (42%); feeling socially isolated (47%); grieving for a life they could not have (49%); and having suicidal thoughts (18%) [24]. In addition, 91% of survey respondents said that control of their symptoms would have a positive impact on their mental and emotional wellbeing [24]. Two patients stated that [24]:

"*It can feel **relentless** and drive you to the **lowest points** where at times, **I have thought that taking my life would be better than the constant pain** or **self-harming would be a diversion from the pain,** and on occasion, **substance misuse would blank out the pain.***"

"*A really **acute flare** can still just get me and take me to the **lowest possible place**. I think the amount of people, myself included, who have done that and said "**I'd rather not be here anymore than live with this relentless pain***"

In a study conducted in Greece, patients with HS (n = 94) were found to have higher anxiety, depression, and loneliness and social isolation scores, and lower self-esteem scores, than healthy controls [53]. Anxiety and depression were the most frequently reported comorbidities in the Global VOICE study, affecting 36.2% and 35.8% of patients with HS, respectively [20]. In the UNITE registry, 31.7% and 19.3% of patients had the probable presence of anxiety or depression (Hospital Anxiety and Depression Scale scores of 11–21), respectively [31]. Similarly, in a US cohort study, 17.7% and 17.4% of adults with HS had anxiety or depression, respectively, at the time of their HS diagnosis, increasing to 25.1% and 24.7%, respectively, two years after diagnosis [37].

Impact of HS on patients' lives

HS has a substantial negative impact on the everyday lives of patients.

The UCB UK patient survey found that 49% of patients reported regularly or constantly experiencing fatigue. Patients reported HS having a considerable to devastating impact on their clothing choices (67%); their social life (55%); their ability to be intimate with someone (66%); their mobility or ability to move comfortably (47%); their ability to exercise and stay active (53%); and their ability to wash and dress themselves (40%) [77].

In the Global VOICE study (n = 1299), many patients reported that HS had caused them to feel very withdrawn (48.6% [n = 631]), very embarrassed (37.3% [n = 485]) or very depressed (35.0%, [n = 455]) either very much or extremely in the past week [20]. Overall, most participants reported that HS had impacted their lives moderately (27.2% [n = 353]) or either very much or extremely (43.3% [n = 563]) in the past week.

The EU5 plus USA survey described above described the areas most affected by HS as being personal appearance and self-confidence (proportion greatly affected: 15.1%, 87/577), mood (12.7%, 73/576), close personal relationships (10.2%, 59/578), feelings about the future (6.8%, 39/573), leisure activities (6.8%, 39/572) and motivation (6.5%, 37/567) [8].

In the Danish survey of patients with HS (n = 421), a substantial proportion reported limitations in daily life, assessed with the EQ-5D-3L; these included problems with pain/discomfort (79%), usual activity (45%), anxiety/depression (40%), mobility (32% of patients) and self-care (16%) [76].

In the UNITE registry, for each item of the DLQI more than 50% of adult patients expressed at least some burden. Patients were especially affected (rated as 'a lot' or 'very much') by dermatological symptoms of the disease including pain (59.2%), how the disease influenced the clothes they wore (56.3%), and the embarrassment and self-consciousness experienced (53.5%). Sexual difficulties and problems with partners, close friends, or relatives were reported to be affected 'a lot' or 'very much' in over 30% of patients [31].

The mean HS Impact Assessment mobility impact score (on a scale of 0–10, with 0 indicating no impact and 10 great impact of HS on quality of life) among patients in the UNITE registry was 3.7 ± 2.9. Of the mobility types assessed (ability to sit, walk, exercise and move arms), the greatest impact was on exercise (5.0 ± 4.0) [31].

Burden and expense for patients of wound care

The 2022 British Dermatological Nursing Group (BDNG) consensus statement describes the substantial impact of wound care on patients' lives [59]. Patients may struggle to apply dressings due to wound locations, while either insecure dressings or the use of adhesives can cause pain and damage. Exudate from HS lesions can cause skin damage and can lead to embarrassing leaks and odour. Many dressings for HS are bulky, restricting movement and leading to patients feeling embarrassed. In addition to wound care being time consuming, issues around dressings can lead to patients avoiding going out in public for long periods of time, impacting on their ability to work, exercise and contribute to society [59].

In of the UCB UK patient survey, 56% of patients reported that finding wound care and dressings can be a problem, with 51% reporting wound care having a negative impact on their social lives and 35% reporting a negative impact on their professional life and career [77]. One patient said [77]:

"*I try not to wear bandages every day. And if I do need them on, I'm putting myself at **risk of infection**. And if I leave them off, I'm **destroying my clothes**, I'm releasing an **odour**, I'm **isolating myself away**. I think it's the most **distressing** one for me.*"

In an international online survey with 908 respondents from 28 countries, 81% of respondents (n = 734) reported that regular dressing changes negatively impacted on their quality of life. Most patients, 82% (n = 744), experienced pain during dressing changes, 16% (n = 142) of patients required five or more dressings daily, and 12% (n = 108) spent over 30 minutes daily tending to wounds [79].

The OHE focus group found that the most appropriate dressings are not routinely prescribed, placing a financial burden on individuals with HS. These out-of-pocket costs are significant, and disproportionately affect black people over white people and women over men [21]. Including transport costs for accessing healthcare services, costs of dressings and

baseline prescription costs, the out-of-pocket cost of HS per person per year was estimated to be £1,500 [21].

Impact of HS on HRQoL

Results from a European multinational study of 4,010 patients with skin diseases indicated that HRQoL impairment in HS is worse than that observed in many skin diseases, and is similar to or worse than that observed in patients with rheumatoid arthritis pain, chronic obstructive pulmonary disease, cancer and cardiovascular disease [38]. Additionally, in a Danish survey, patients with HS treated at a hospital dermatology department (n = 421; disease severity not reported) had substantially lower mean EQ-5D-3L index scores than the general population (0.705 vs 0.887) [76].

Studies have shown a relationship between HS disease severity and HRQoL. Dermatology Life Quality Index (DLQI) scores worsened with increasing disease severity in adult patients with HS enrolled in the UNITE registry (n = 529): mean ± SD DLQI total scores in Hurley stages I, II and III were 8.8 ± 7.3, 11.6 ± 7.5 and 15.7 ± 8.2, respectively [31]. In a systematic literature review, six studies that compared DLQI total scores across different disease severities all showed higher DLQI scores in patients with severe HS than in those with moderate or mild HS according to Hurley stage [80].

Impact of HS on family members

HS can have a significant impact on the families of people with HS. In a UCB survey of UK patients (n=59) in March 2024, 39% of patients reported constantly or regularly feeling like a burden to their friends and family, and 80% of people reporting that relief of their symptoms would positively impact their relationships with friends and family. In addition to the effect of HS on patients, two Spanish studies have found that the disease also reduces the quality of life of family members, particularly as a result of anxiety, depression and sexual dysfunction [81, 82]. Partners may experience a wide range of emotional and social effects as a result of the disease, with greater disease severity being significantly correlated with reduced quality of life of the partners of people with HS [21, 83]. In a Polish study, the partners of people with HS in Hurley stages I, II and III had mean Family Dermatology Life Quality Index (FDLQI) scores of 4.9 (small impairment), 9.4 (moderate impairment) and 11.8 (very large impairment), respectively [83]. The impact of dermatological conditions on patients' partners may be physical or economic as well as psychosocial [83-87]. Relatives living with and caring for a dermatological patient can experience detrimental effects in aspects of their education, career, social life, interpersonal relations and finances [83, 86, 87].

B.1.3.1.5 Impact on the NHS, society and employment

Burden on the NHS

A retrospective cohort study of 11,359 patients receiving inpatient treatment for HS in England, conducted using Hospital Episode Statistics (HES) data, found that, over a 5.5-year period, 71% had attended at least one general surgery (type of surgery was not reported) [88]. These patients had 303,204 outpatient attendances (for example, dermatology, plastic surgery and general surgery) over the length of the study, a mean of

27.1 attendances per patient over the course of the study and a mean of 3.95 outpatient attendances per patient per year [88]. Further details of hospital attendances over the course of the study are shown in Table 5. A 2023 OHE report estimated that the direct annual cost to the NHS is £4,900 per person with HS, with comorbidities adding a further cost of £1,200–2,100 per person per year [21].

Table 5 Hospital attendances of 11,359 patients with HS in England over a 5.5-year period [88]

	Total	Per patient per year
Number of outpatient attendances	303,204	3.95
Number of inpatient attendances	65,544	–
Non-elective inpatient procedures	7202	0.35
Elective procedures	4128	0.09
Day case procedures	9790	0.42
Number of accident and emergency attendances	43,773	0.57

Impact of HS on work and productivity

HS has a negative impact on the professional lives of patients. It affects people during their peak formative and productive years, and is associated with high unemployment, slower income growth, and a higher risk of leaving the workforce [21].

HS has a significant and negative impact on broader life and career fulfilment. In the UCB UK patient survey, patients reported HS having a considerable to devastating impact on their ability to participate in education (41%, n=51); ability to work or hold down a job (34% n=56); productivity at work or at home (46% n=57); and their ability to fulfil their career aspirations (36% n=58) [77]. In addition, 74% of patients said that control of their symptoms would have a positive impact on their financial situation and career aspirations [24]. Two patients stated that [24]:

"*I'm 30. I've never shared this with people before, but I've* ***never had a job***, ***never worked***. ***At every point, HS has interrupted my life***"

"*My* ***mobility is pretty limited***, *so* ***I can't work*** *because it causes me so much* ***pain***. *I haven't been able to work for three or four years now because of the pain.*"

The 2022 BDNG consensus statement noted in particular that during flares, patients often struggle to carry out simple day-to-day tasks and may have to take time off work [59].

In a 2022 survey of 43 people with HS in the UK, 37.2% of respondents were in receipt of temporary or long-term illness benefit, and 11.6% were unemployed, compared with 14.4% and 3.8%, respectively, of the general population ($p < 0.001$ for receipt of illness benefit or unemployment among people with HS versus the general population) [89]. Similarly, in a Danish study, the unemployment rate of adult HS patients eligible for a job was 25.1%, compared with 6.2% in the general population [90].

Work productivity can also be impacted by HS. In a study of 200 patients with HS in Hungary, the patients missed, on average, 26 and 63 days from work annually owing to absenteeism and presenteeism, respectively [91]. Among 57 employed patients in a Danish study, 21.2% reported missing work and 60.4% reported loss of work productivity during the preceding week because of HS [92]. In a cohort of 481 patients with HS in Germany, the rate of unemployment (12.6%) was two-fold higher than that in the general German population, and mean HS-related absenteeism and presenteeism were 13.3% and 25.2%, respectively [93]. The international, prospective, observational HS disease registry UNITE enrolled patients with active HS from 12 countries (Australia, Canada, the Czech Republic, France, Germany, Greece, Hungary, Italy, the Netherlands, Spain, Switzerland and the USA). In total, 319 of 529 enrolled adult patients (60.3%) reported being employed and rates of absenteeism and presenteeism in the employed patients were 9.9% and 29.8%, respectively [31].

Cost to society

The 2023 OHE report estimated a lost societal potential of £12,300 per year per person diagnosed with HS, as a result of productivity losses, out-of-pocket costs and healthcare costs (Table 6) [21, 94].

Table 6 OHE estimate of the UK societal cost of HS

	Average annual cost in the UK per person with HS	Aggregate annual cost in the UK among HS prevalence cohort
Cost to society (productivity losses)	£12,320	£2.4 billion
Out-of-pocket costs to people with HS	£1,500	£288 million
Costs associated with comorbidities	£1,236	£238 million
Direct healthcare costs to NHS	£4,867	£935 million
Total	**£19,923**	**£3.83 billion**

The prevalence cohort in the OHE analysis was an estimated 192,000 people living with a confirmed HS diagnosis in the UK. The OHE analysis was published in 2023, but the year for costs was not explicitly reported.
HS, hidradenitis suppurativa; OHE, Office of Health Economics.

B.1.3.2 Aetiology and bimekizumab mechanism of action

Aetiology and inflammatory pathways

HS is primarily known as a disorder of follicular occlusion. However, increased levels of inflammatory cytokines have been implicated as the underlying cause of dermal inflammation and follicular occlusion [26]. HS is a biologically complex neutrophilic disease. Several inflammatory pathways are highly active in HS; in particular, the interleukin (IL)-17 and tumour necrosis factor (TNF)-α pro-inflammatory cytokines are implicated in the disease [25, 27].

After rupture of an occluded follicle, its contents are released. This leads to the inflammasome-mediated release of IL-1β, predominantly by tissue macrophages, and further

downstream cytokine signalling, including by the IL-17 cytokines and TNFα [25, 95, 96]. T helper 17 (Th17) cells expressing IL-17A and IL-17F, two of the key pro-inflammatory cytokines involved in HS, are expanded even in early HS lesions [96, 97], and are strongly implicated in established self-sustaining clinical disease [26]. IL-17A and IL-17F activate surrounding skin cells (specifically keratinocytes, the primary type of cell found in the epidermis) resulting in recruitment of neutrophils and elevation of IL-17A and IL-17F production by Th17 cells in a feedback loop [25]. Over time, this results in the formation of inflammatory nodules, abscesses, and eventually DTs and scar [27].

IL-17 signalling

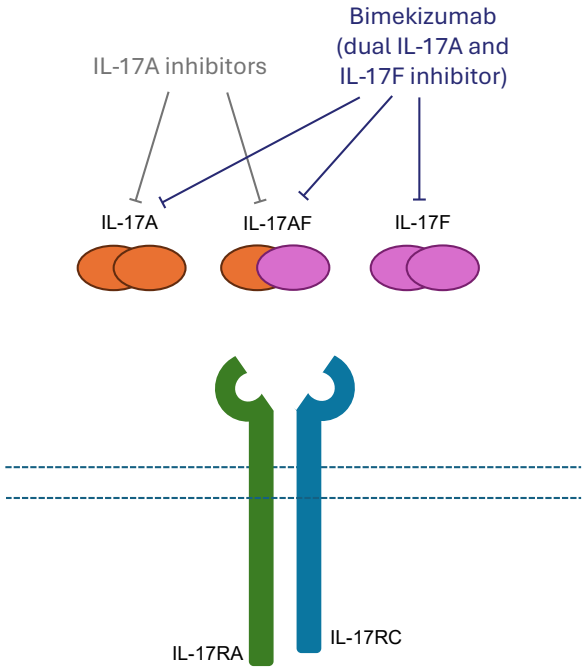
IL-17A and IL-17F are often co-expressed, and are secreted predominantly by Th17 cells [25, 96]. IL-17A and IL-17F can bind to receptors as homodimers or as heterodimers (IL-17A/F) [25]. The main receptor for IL-17A and IL-17F signalling is a heterodimer of IL-17 receptor A (IL-17RA) and IL-17RC (although signalling through other receptor complexes has also been reported) [25].

Bimekizumab mechanism of action

Bimekizumab is a humanised immunoglobulin G1 (IgG1)/κ monoclonal antibody. Unlike other IL-17 biologics such as secukinumab and ixekizumab that inhibit the biological function of IL-17A homodimers and IL-17A/F heterodimers, bimekizumab selectively inhibits IL-17A homodimers, IL-17F homodimers and IL-17A/F heterodimers, blocking their interaction with the IL-17RA/IL-17RC receptor complex (Figure 2) [39]. Unlike most anti-cytokine monoclonal antibodies, bimekizumab was deliberately designed to inhibit more than one cytokine and capture biological redundancy in IL-17–mediated inflammatory diseases. Both IL-17A and IL-17F are co-expressed at sites of inflammation and single cell work in inflammatory lesions (psoriasis and HS) has shown that there are distinct IL-17 secreting cells (e.g., those that produce IL-17A, those that produce both IL-17A and IL-17F and those that produce only IL-17F) [97].

In human cells, inhibiting both IL-17A and IL-17F with bimekizumab has been shown to suppress inflammatory gene expression and neutrophil migration to a greater degree than blockade of IL-17A alone [4]. By inhibiting both of these key pro-inflammatory cytokines, bimekizumab disrupts the Th17 cell feedback loop, reducing inflammation and improving disease symptoms [39, 98]. This supports the rationale for dual inhibition of IL-17A and IL-17F in HS. These *in vitro* data are consistent with the BE RADIANT study in patients with psoriasis, in which inhibition of both cytokines IL-17A and IL-17F was superior at week 16 compared to inhibition of Il-17A alone with secukinumab, as assessed by PASI100 response rates [99].

Figure 2 IL-17A and IL-17F signalling and bimekizumab mechanism of action



IL-17, interleukin 17; IL-17R, interleukin 17 receptor.

Source: Oliveira et al. [100]2021 [100].

B.1.3.3 Clinical pathway of care for hidradenitis suppurativa

Treatment guidelines

UK guidelines have been published by the British Association of Dermatologists (BAD; in 2018) [43] and the Primary Care Dermatology Society (PCDS; in 2023) [72].

Conventional systemic therapy

Guidelines recommend initial disease staging using the Hurley system [43, 72], with immediate referral to secondary care in the case of stage III disease [43]. Initial treatment of HS may consist of topical antiseptics and topical antibiotics (e.g., clindamycin) [43, 72]. Weight loss and smoking cessation advice may also be offered alongside initial disease management [43, 101]. If initial treatment is unsuccessful, the use of oral tetracyclines for 12 weeks is recommended [43, 72], followed by oral clindamycin and rifampicin when oral tetracyclines have not worked (or instead of tetracyclines for stage III disease). Retinoids such as acitretin or the anti-inflammatory antibiotic, dapsone, may be considered when earlier treatments have not worked [43]. However, these therapies are often also unsuccessful, and dapsone use can be problematic due to the initial requirement for weekly blood tests [102].

Biological therapies

For patients for whom conventional systemic treatment is ineffective, BAD guidelines recommend surgical intervention (described below) or the TNF inhibitor (TNFi) adalimumab [43], which has limited effectiveness, as described below.

NICE TA392 recommends adalimumab for moderate to severe HS in adults whose condition has not responded to conventional systemic treatment [42]. However, for approximately half of patients, adalimumab treatment does not lead to a clinical response (defined as HiSCR50), as shown in the phase 3 trials of adalimumab [46]. Adalimumab may also work at first and then stop working (secondary failure) [44, 45]. For example, in the phase 3 trials of adalimumab, approximately half of patients treated with adalimumab weekly who had HiSCR50 at week 12 had lost this response by week 36 (PIONEER I, 47.6% [N = 21]; PIONEER II, 54.8% [N = 31]; non-responder imputation; it should be noted that the protocol mandated discontinuation after 50% loss of the 12-week improvement, even if the loss was temporary, and these results are not directly comparable to other phase 3 trials) [46]. UCB also surveyed 4 dermatologists practising in England, and all said that at 1 year about 50% of patients treated with adalimumab are achieving HiSCR25. In a retrospective study of 104 patients with HS treated with adalimumab at two dermatology centres in the Netherlands, 21 patients (20%) discontinued treatment due to secondary non-response [47]. Including all reasons for discontinuation, only 56% of patients were still using adalimumab after 12 months [47]. In addition, clinical expert opinion (obtained during an HS advisory board) suggests that TNFi therapies may be contraindicated for 5–10% of patients.

Recently, NICE TA935 has recommended secukinumab as an option for treating active moderate to severe HS in adults when their disease has not responded well enough to conventional systemic treatment, only if adalimumab is not suitable, did not work or has stopped working [44]. The recommended dose of secukinumab is 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing [103]. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks [103]. In the secukinumab phase 3 trials SUNSHINE and SUNRISE, respectively, 45% and 42% of patients treated with secukinumab 300 mg every 2 weeks (Q2W) had a HiSCR50 response at week 16; however, across secukinumab Q2W and Q4W treatment groups, 16–24% of patients with a clinical response at week 16 did not maintain their response at week 52 [48].

Real-world data from the UNITE 4-year, global, prospective, observational, HS disease registry suggested that consistent biologic use (12 weeks or more) was associated with a reduced requirement for acute procedural interventions, systemic medications, and healthcare utilisation. However, the analysis was limited to the 6-month periods before, during and after initiation of the biologic; longer-term outcomes were not reported [104].

Wound care

Patients may routinely need dressings for pus-producing abscesses and DTs [43, 72]. Multiple dressing types may be required, depending on the type of lesions and their locations (HS mainly affects skin folds) and patients' individual preferences. For example, patients with HS will often have wounds that leak malodorous fluid. These patients require dressings that are highly absorbent, deodorising, gentle on the skin and antimicrobial [59]. Patients may also need dressings for post-surgical wound care [105]; surgical treatment of HS is described below.

Antibiotics

Antibiotic monotherapy is possible for mild disease, but in advanced disease the role of antibiotics is adjunctive [106]. In clinical practice, antibiotics may be used for the majority of patients. For example, in a recent survey in France, more than 90% of dermatologists reported prescribing antibiotics for flares in Hurley stage I or II, 83% reported prescribing antibiotics for flares in Hurley stage III, and 80% reported prescribing background antibiotics (for preventive treatment or after acute care) to patients with Hurley stage II or III HS [107]. Advice obtained from six UK clinicians (four consultant dermatologists, one plastic surgeon and one general practitioner) at an HS advisory board suggests that antibiotic use is similar in the UK.

Best supportive care

For patients whose disease does not respond to adalimumab or secukinumab, best supportive care (BSC) would be used, which includes surgical procedures, antibiotics, retinoids, dapsone, ciclosporin and anti-androgens, and may include some continued use of adalimumab (see section B.3.2.3.3).

Surgery

Surgical treatments range from incision and drainage of individual lesions to wide local excision [108]. As a result of late diagnosis and delayed use of biologics (see section B.1.3.1.2), lesions and scarring may be present that cannot be reversed by medical treatment – in some cases, the disease can be so widespread at diagnosis that surgery is also not an option [56].

Even where biological therapy is effective, both medical and then surgical treatment is often needed to achieve optimal disease control; furthermore, combined biological and surgical treatment can lead to improved outcomes compared with surgery alone (see below). Advice from UK clinicians (as described above) suggests that surgery sometimes cannot be carried out on active sites of inflammation, and surgery to address damage due to HS may only be an option after biological therapy has been initiated.

In clinical practice, surgery and biological therapy may be used together, and there is evidence that this may lead to higher response rates than surgery alone: in the SHARPS trial, patients undergoing wide-excision surgery followed by secondary intention healing were more likely to achieve HiSCR50 when also treated with adalimumab, compared with those receiving placebo [109]. UK clinicians in two advisory boards emphasised that biologic use improves surgery outcomes and makes surgery an option for some patients who would otherwise be unable to have it by reducing inflammation. Further research is needed on the long-term outcomes of biologic and surgical combination therapy. Results from the SUNSHINE and SUNRISE trials of secukinumab suggest that continuation of secukinumab treatment in patients undergoing surgery does not pose an undue risk of infections; the proportion of patients without treatment interruption who had adverse events (AEs) categorised under “Infections and Infestations” within 30 days post-surgery was 18.3% [110].

A survey of 477 surgeons in the UK and the Netherlands (19 of 22 participating units were in the UK) was conducted in 2017–2018, and found that for limited HS, regardless of location,

the preferred procedure was excision of disease and direct closure. For more extensive HS, the preferred surgical options varied according to HS location [101]. For extensive HS in the groin, the most commonly selected option was excision and split skin grafting, while for extensive axillary disease excision and either split skin grafting or reconstruction with an axial flap was preferred. There was no clear preference for which surgical procedure to use in the case of extensive HS of the breast. Non-surgical procedures (electrocautery and laser treatment) were rarely used by UK respondents [101].

Limitations of current therapies

Patients with moderate to severe HS need additional treatment options that are well tolerated and effective. A prospective survey study of 1,299 people with HS globally (the Global VOICE study; conducted in 2017–2018) found that around 46% of people with moderate to severe HS were not satisfied with their current treatment [20]. The main reasons for dissatisfaction were poor efficacy (42%) and adverse events (19%) [20].

Although the biological therapies adalimumab and secukinumab are approved for the treatment of HS, as described above, these agents do not lead to a clinical response for around half of patients, and some patients lose treatment responses over time: 16–24% of those with HiSCR50 at week 16 in the secukinumab phase 3 trials and more than half of those with HiSCR50 at week 12 in the adalimumab phase 3 trials lost clinical response (as described above, there results are not directly comparable with one another) [44-48]. Real-world data from the UNITE registry suggest that consistent biologic use (12 weeks or more) may reduce the requirement for acute procedural interventions, systemic medications, and healthcare utilisation. However, the analysis was limited to the 6-month periods before, during and after initiation of the biologic; longer-term outcomes were not reported [104].

According to advice received from UK clinicians in a survey, many patients in clinical practice remain on treatment with adalimumab with an HiSCR25 response (or less) because there are insufficient (more effective) alternative treatment options, leading to a high HRQoL burden and greater NHS resource use.

If HS cannot be well controlled with medication alone, the main treatment option for most patients is surgery [60]. Although effective in removing lesions, surgery does not address the underlying inflammation driving HS disease activity. Additionally, HS may recur post-operatively; for example, in cohort studies in the France and the USA, 35% and 41% of procedures were followed by recurrence at the same site [111, 112]. Furthermore, advice from UK clinicians who took part in a UK advisory board suggests that surgery sometimes cannot be carried out on active sites of inflammation. In UK practice, there may be a limit to the number of surgical procedures patients can undergo, even when these are effective. Following surgery, patients require treatment with powerful antibiotics to prevent post-surgical infection.

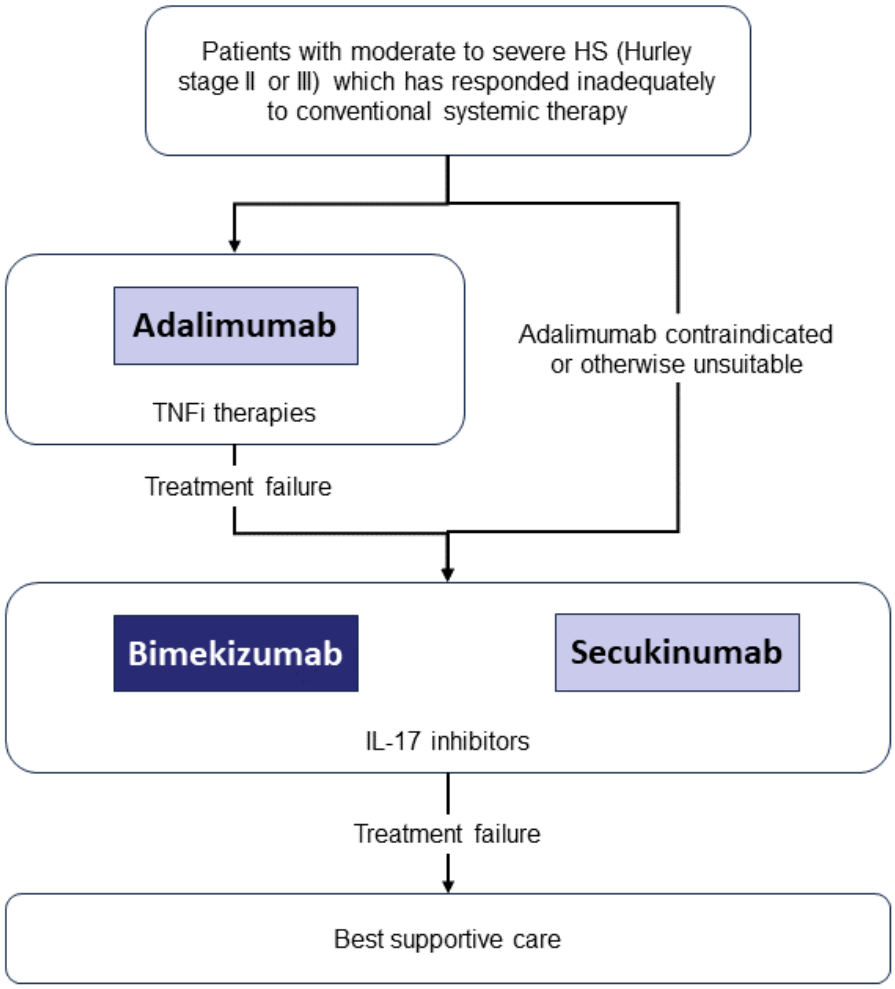
In the Global VOICE study, 35% of patients reported being dissatisfied with procedural treatments [20]. Biologic use may improve surgical outcomes [109], but there is a lack of long-term data to support this.

Accordingly, for patients with moderate to severe HS there remains a need for additional well-tolerated, efficacious therapies.

B.1.3.4 Proposed positioning of bimekizumab in the treatment pathway

The proposed positioning of bimekizumab in the treatment of moderate to severe HS is for adult patients who have an inadequate response to conventional systemic treatments and for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment (Figure 3). This positioning would place bimekizumab alongside secukinumab in the treatment pathway.

Figure 3 Anticipated treatment pathway for patients with moderate to severe HS which has responded inadequately to conventional systemic therapy, including proposed positioning of bimekizumab



HS, hidradenitis suppurativa; IL, interleukin; TNFi, tumour necrosis factor inhibitor.

B.1.4 Equality considerations

The prevalence of HS is higher among women than men, and among people with an African–Caribbean background compared with those with a European background (see section B.1.3.1.3).

It is not anticipated that this appraisal will exclude from consideration any people protected by the equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Summary

Clinical trial evidence

- The efficacy and safety of bimekizumab in the treatment of moderate to severe HS has been investigated in two 48-week phase 3 double-blind, randomised, placebo-controlled trials (RCTs), BE HEARD I and BE HEARD II.
- The treatment regimen in the BE HEARD trials most relevant to the decision problem is 16 weeks of initial therapy with bimekizumab 320 mg every 2 weeks (Q2W) followed by maintenance therapy with bimekizumab 320 mg every 4 weeks (Q4W; bimekizumab 320 mg Q2W/Q4W).
- Data for 96 weeks of treatment with bimekizumab from the BE HEARD EXT open-label extension study are also included in this submission.
- Additional evidence is available from subgroup analyses of the BE HEARD trials and from a phase 2 study assessing bimekizumab.
- Indirect comparative evidence is provided from a network meta-analysis (NMA) and a matching-adjusted indirect comparison (MAIC).

Analyses presented

- In the prespecified analysis of the BE HEARD trials, patients who had received a systemic antibiotic for any reason (all-ABX) during the study period, as well as those who discontinued due to lack of efficacy or AEs, were deemed to have experienced an intercurrent event. Outcomes for patients who had experienced an intercurrent event were imputed as non-response at all subsequent visits for binary endpoints (modified non-responder imputation [mNRI] for all-ABX), and were treated as missing, and then imputed, for continuous endpoints (multiple imputation [MI] for all-ABX). The results of the prespecified analysis are presented in Appendix D.4 for primary and key secondary endpoints.
- BE HEARD trial data presented in this section are from a post hoc analysis (for binary endpoints, mNRI for HS-ABX; for continuous endpoints, MI for HS-ABX). In this analysis, receipt of a systemic antibiotic was considered to be an intercurrent event only if used for HS rescue, as defined by the principal investigator. Those who discontinued due to lack of efficacy or AEs, were also deemed to have experienced an intercurrent event.
- Observed case (OC) data are also provided in this section.
- In general, for the primary and key secondary endpoints at week 16 all patients receiving initial treatment with bimekizumab 320 mg Q2W were analysed as one group (with some exceptions to enable use of published material to be prioritised). From week 16, patients taking bimekizumab 320 mg Q2W went on to receive either bimekizumab 320 mg Q2W (Q2W/Q2W) or bimekizumab 320 mg Q4W (Q2W/Q4W) maintenance therapy. These regimens are analysed separately to assess the effect of the anticipated bimekizumab treatment regimen (320 mg Q2W/Q4W).
- Primary and key secondary endpoint results are reported for the individual BE HEARD trials. Where available, analyses pooled across the trials are shown for other endpoints.

Clinical efficacy at week 16

- The proportion of patients with a HiSCR50 response at week 16 was the primary endpoint of the BE HEARD trials. Both BE HEARD trials met their primary endpoints in the prespecified mNRI for all-ABX analysis (BE HEARD I: bimekizumab 320 mg

combined Q2W groups, 47.8%; placebo, 28.7%; $p = 0.006$; BE HEARD II: bimekizumab 320 mg combined Q2W groups, 52.0%; placebo, 32.2%; $p = 0.003$).
- Results also favoured bimekizumab in the mNRI for HS-ABX analysis assessing HiSCR50 at week 16 (BE HEARD I: bimekizumab 320 mg combined Q2W groups, 55.2%; placebo, 34.0%; BE HEARD II: bimekizumab 320 mg combined Q2W groups, 58.7%; placebo 32.3%).
- In addition, patients were more likely to achieve week 16 HiSCR25, HiSCR75, HiSCR90 and HiSCR100 responses with bimekizumab Q2W/Q4W than with placebo (mNRI for HS-ABX analyses).
- HiSCR25 – pooled BE HEARD I and BE HEARD II population: bimekizumab 320 mg Q2W/Q4W group, 65.5%; placebo, 43.6%.
- HiSCR75 – BE HEARD I: bimekizumab 320 mg Q2W/Q4W group, 37.4%; placebo, 18.3%; BE HEARD II: bimekizumab 320 mg Q2W/Q4W group, 40.5%; placebo 15.7%.
- HiSCR90 – pooled BE HEARD I and BE HEARD II population: bimekizumab 320 mg Q2W/Q4W group, 22.0%; placebo, 8.5%.
- HiSCR100 – pooled BE HEARD I and BE HEARD II population: bimekizumab 320 mg Q2W/Q4W group, 16.6%; placebo, 5.6%.

Clinical efficacy during maintenance treatment

- Most patients receiving bimekizumab 320 mg Q2W/Q4W retained their week 16 HiSCR responses to initial treatment with bimekizumab 320 mg Q2W after 32 weeks of subsequent bimekizumab 320 mg Q4W treatment (OC analysis; pooled BE HEARD population): among patients with a week 16 HiSCR50 response, 88.5% maintained this response at week 48; in addition, 88.3% of patients with a week 16 HiSCR75 response retained it at week 48.

Efficacy measured with IHS4

- Treatment with bimekizumab 320 mg Q2W/Q4W was associated with a substantial reduction in disease severity by week 16, as measured with the IHS4 (pooled BE HEARD population; MI for HS-ABX). The reduction in IHS4 disease severity seen at week 16 was sustained and further improved during maintenance treatment.
- The proportion of patients with severe disease (≥ 11 points) in the bimekizumab 320 mg Q2W/Q4W group at baseline was 88.4%, with the remaining 11.6% having moderate disease (4–10 points).
- At week 16, the proportion of patients with severe disease had reduced to 47.3%, with 24.6% now having mild disease (≤ 3 points).
- At week 48, 36.4% of patients had severe disease, and 38.3% had mild disease.
- These improvements in IHS4 disease severity demonstrate the benefits to patients of bimekizumab 320 mg Q2W/Q4W treatment in terms of DTs as well as inflammatory nodules and abscesses.

Patient-reported outcomes

- Patients treated with bimekizumab 320 mg Q2W had larger mean improvements in worst daily skin pain (Hidradenitis Suppurativa Symptom Daily Diary [HSSDD] worst skin pain item) at week 16 than those receiving placebo (mean change from baseline to week 16, BE HEARD I: combined bimekizumab 320 mg Q2W groups, −1.98; placebo, −0.92; BE HEARD II, −1.87; placebo, −0.45).
- In addition, in the combined bimekizumab 320 mg Q2W groups, 36.7% of patients in BE HEARD I and 36.7% of those in BE HEARD II had a skin pain response (≥ 3-point decrease from baseline in HSSDD weekly worst skin pain score among study participants with a score of ≥ 3 at baseline) at week 16, compared with 16.1% and 11.1% in the two placebo groups.
- Patients treated with bimekizumab 320 mg Q2W were more likely than those receiving placebo to achieve week 16 NRS30 (a ≥ 30% reduction and reduction of ≥ 2 units from

baseline in HSSDD weekly worst skin pain NRS score, assessed in patients with a baseline score of ≥ 3) skin pain responses (49.9% vs 26.9%).
- Treatment with bimekizumab 320 mg Q2W was also associated with improvements in HRQoL, with 56.5% of patients who had baseline DLQI ≥ 4 achieving a minimal clinically important difference (MCID; ≥ 4-point improvement) after 16 weeks.
- Patients treated with bimekizumab 320 mg experienced substantial improvements in HiSQOL scores. Across all bimekizumab 320 mg groups, the HiSQOL total score improved by 11.0 points from baseline to week 16, compared with an improvement of 5.8 points in the placebo group. Among patients treated with bimekizumab 320 mg, the improvement increased to 13.4 points at week 48.

Extension study

- Among patients treated with bimekizumab 320 mg Q2W/Q4W in the BE HEARD trials who had a HiSCR90 response on average over weeks 36–44, HiSCR50, HiSCR75, HiSCR90, HiSCR100 and IHS4-55 responses were generally maintained during a further 48 weeks of maintenance treatment with bimekizumab 320 mg Q4W.
- Notably, after 96 weeks of treatment with the bimekizumab 320 mg Q2W/Q4W/Q4W regimen in this patient group, [redacted] of patients had a HiSCR100 response and [redacted] of patients had an IHS4-55 response.

Subgroup analyses

- Subgroup analyses found bimekizumab 320 mg Q2W/Q4W to be more efficacious than placebo in inducing HiSCR50 responses at week 16 and week 48, regardless of patients' prior biologic use, disease severity, weight and sex.

Network meta-analysis

- An NMA was conducted to estimate the relative efficacy of bimekizumab, secukinumab, adalimumab and placebo at week 12–16 (the NMA results for adalimumab are not presented in this section as a comparison with adalimumab is not considered within scope).
- The NMA results showed that bimekizumab 320 mg Q2W was significantly more likely than secukinumab 300 mg Q2W or Q4W to provide HiSCR50 (OR [95% CrI] vs secukinumab 300 mg Q2W, 1.70 [1.16–2.45]), HiSCR75 (2.02 [1.38–3.20]), HiSCR90 (1.86 [1.30–2.75]), HiSCR100 (1.77 [1.12–2.77]), and IHS4-55 (1.96 [1.22–3.17]) responses, as well as leading to a statistically significantly greater decrease in IHS4 score (mean difference [95% CrI] vs secukinumab 300 mg Q2W, −4.35 [−8.53, −0.17]).
- Bimekizumab 320 mg Q2W was associated with a statistically significantly greater mean decrease in DT count at week 16, compared with secukinumab 300 mg Q4W (mean difference, −1.14% [−1.97%, −0.34%]), and a numerically greater reduction compared with secukinumab 300 mg Q2W.
- Treatment with bimekizumab 320 mg Q2W was also associated with a numerically larger mean percentage reduction in AN count and a numerically greater likelihood of achieving an NRS30 skin pain responses (a ≥ 30% reduction and reduction of ≥ 2 units from baseline in HSSDD weekly worst skin pain NRS score, assessed in patients with a baseline score of ≥ 3).
- Among biologic-experienced patients, treatment with bimekizumab 320 mg Q2W was numerically more likely than secukinumab 300 mg Q2W or Q4W to generate HiSCR50 responses (OR [95% CrI] vs secukinumab 300 mg Q2W, 1.97 [0.67–6.27]), and was associated with a numerically greater mean percentage reduction in AN count (mean difference [95% CrI] vs secukinumab 300 mg Q2W, −16.33% [−45.63%, 12.62%]).
- For all of the above endpoints, bimekizumab 320 mg Q2W had the highest probability of being ranked as the most effective treatment at week 16.

Matching-adjusted indirect comparison

- Due to the lack of a placebo arm after the initial treatment periods in the relevant trials, an unanchored MAIC was conducted to compare the efficacy of bimekizumab and secukinumab at week 48–52.
- The MAIC found that, compared with the secukinumab 300 mg Q2W group, patients treated with bimekizumab 320 mg Q2W/Q4W had statistically significantly higher odds of achieving HiSCR50 (OR [95% CI]: HiSCR50, 2.00 [1.42–2.80]; HiSCR75, 1.91 [1.35–2.70]; HiSCR90, 2.05 [1.39–3.04]).
- Similar, statistically significantly results were seen in the comparison with secukinumab 300 mg Q4W (OR [95% CI], 2.06 [1.45, 2.92]), HiSCR75 (OR [95% CI], 2.13 [1.49–3.05]) and HiSCR90 (OR [95% CI], 2.04 [1.36–3.04]).

Safety

- Overall, the results of the safety analyses show that bimekizumab 320 mg Q2W/Q4W is generally well tolerated.
- The safety data observed in the BE HEARD trials were generally consistent with the known safety profile of bimekizumab in other indications, and no new safety signals were identified.
- In line with the bimekizumab mechanism of action, an increased incidence of oral candidiasis was seen with bimekizumab, compared with placebo – most cases were mild to moderate, able to be resolved with appropriate antifungal therapy, and did not lead to discontinuation.
- Across the bimekizumab HS phase 3 clinical trial programme including data up to week 48, one patient with significant cardiovascular history died of congestive heart failure, which was considered unrelated to bimekizumab treatment by the study investigator (BE HEARD I: bimekizumab 320 mg Q2W/Q2W group).

B.2.1 Identification and selection of relevant studies

Identification and selection of relevant clinical evidence is described in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Included clinical trials

The main sources of evidence in this submission are BE HEARD I (NCT04242446) and BE HEARD II (NCT04242498), two identical randomised, placebo-controlled, double-blind, multicentre phase 3 trials evaluating the efficacy and safety of bimekizumab in moderate to severe HS (Table 7) [1, 2, 113, 114]. These trials provide evidence for the clinical efficacy and safety of bimekizumab.

Table 7 Clinical effectiveness evidence

Study	**BE HEARD I (NCT04242446) and BE HEARD II (NCT04242498)**
Study design	48-week randomised, double-blind, placebo-controlled phase 3 trials with 16-week initial treatment period and 32-week maintenance treatment period
Population	Adult patients with a diagnosis of HS with ≥ 5 inflammatory lesions (AN) at least 6 months prior to baseline HS lesions present in at least 2 distinct anatomic areas, one of which is at least Hurley stage II

Study	BE HEARD I (NCT04242446) and BE HEARD II (NCT04242498)		
	Moderate to severe HS defined as a total of ≥ 5 inflammatory lesions History of inadequate response to a course of a systemic antibiotics for treatment of HS Patients with > 20 DTs were excluded		
Intervention(s)	Bimekizumab 320 mg Q2W Bimekizumab 320 mg Q4W Bimekizumab 320 mg Q2W initial treatment up to week 16, followed by bimekizumab 320 mg Q4W maintenance treatment		
Comparator(s)	Placebo initial treatment up to week 16, followed by bimekizumab 320 mg Q2W maintenance treatment		
Supports application for marketing authorisation	Yes	**Used in the economic model**	Yes
Rationale if study not used in model	The BE HEARD trials are the main source of clinical evidence for bimekizumab in HS		
Reported outcomes specified in the decision problem	Clinical response: **HiSCR25, HiSCR50**, **HiSCR75**, **HiSCR90**, HiSCR100 Disease severity: IHS4, IHS4-55, HS lesion counts, HSSDD symptoms, flare Discomfort and pain: HSSDD worst and average skin pain, HSSQ HRQoL: DLQI, **EQ-5D-3L**, HiSQOL **AEs**		

Outcomes in **bold** are incorporated into the economic model.
AE, adverse event; AN, abscess and inflammatory nodule; DLQI, Dermatology Life Quality Index; DT, draining tunnel; EQ-5D-3L, 3-level, 5-dimension EuroQol questionnaire; HiSCR, hidradenitis suppurativa clinical response; HiSQOL, Hidradenitis Suppurativa Quality of Life; HS, hidradenitis suppurativa; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary; HSSQ, HS symptom questionnaire; IHS4, International Hidradenitis Suppurativa Severity Score System; Q2W, every 2 weeks; Q4W, every 4 weeks.
Sources: Kimball *et al.* 2023, AAD presentation [115]; BE HEARD CSRs [1, 2].

Additional evidence is available from a phase 2 study (NCT03248531) comparing bimekizumab with placebo and including a comparative adalimumab arm (the study was not powered to compare bimekizumab with adalimumab) [116]. Because data from phase 3 trials are available, the phase 2 results are not described in detail in this document. However, the results of this phase 2 trial are summarised in section B.2.6.10.1 [116], and the trial is included in the network meta-analysis (NMA) described in section B.2.9. Results from a French real-world cohort are also summarised in section B.2.6.10.3.

Open-label extension

Patients in the phase 3 trials were eligible to transfer to a long-term open-label extension study (BE HEARD EXT; NCT04901195) [117]. Preliminary data for this study are available and are summarised in section B.2.6.10.1.

Subgroup analyses of clinical efficacy

Supporting evidence is provided by subgroup analyses of the BE HEARD I and BE HEARD II trials, which were conducted according to prior biologic use, systemic antibiotic use at

randomisation, baseline Hurley stage, weight, sex and race (section B.2.7). Subgroup analyses according to weight, sex and race are important because of the association between obesity and HS and the increased prevalence of HS seen in women compared with men and in people with an African–Caribbean background, compared with other groups [70].

Economic model inputs

Clinical outcomes in the economic model (section B.3) are based on a comprehensive NMA of evidence from clinical trials. The week 12–16 endpoints included in the NMA and reported in this submission are: HiSCR50, HiSCR75, HiSCR90, HiSCR100 (all mNRI for HS-ABX), IHS4-55 (mNRI for HS-ABX), change from baseline in IHS4 total score (MI for HS-ABX), percentage change in AN count (MI for HS-ABX), absolute change in DT count (MI for HS-ABX) and skin pain response (mNRI for HS-ABX; NRS30; see section B.2.3.1.6). HiSCR50 and percentage change in AN count results are also presented for the subgroup of patients with prior biologic experience.

Because of the lack of a placebo arm after the initial treatment periods in the relevant trials, an unanchored MAIC was conducted to compare the efficacy of bimekizumab and secukinumab at week 48; the MAIC outcomes reported in this submission are HiSCR50, HiSCR75 and HiSCR90 (all NRI).

Health states in the economic model are based on HiSCR25, HiSCR50, HiSCR75 and HiSCR90 responses; EQ-5D-3L data are also included in the model, and adverse event (AE) data are included in a sensitivity analysis (see sections B.2.3.1.6 and B.2.10).

Data sources

Data from the phase 3 trials are taken from two clinical study reports (CSRs) [1, 2], one clinical trial protocol [118], three clinicaltrials.gov records [113, 114, 117], internal clinical data tables [119-128] and 14 conference presentations [115, 129-141].

Intercurrent event handling

The management of intercurrent events is described in detail in section B.2.4.3.

In the analysis specified in the trial protocols, which were developed in accordance with US Food and Drug Administration (FDA) guidelines and advice, intercurrent events were defined as discontinuation due to lack of efficacy, discontinuation due to adverse events or any use of systemic antibiotics (all-ABX). Results for this prespecified analysis of the BE HEARD primary and key secondary endpoints, together with their statistical significance, are shown in Appendix D.4.

At baseline, antibiotic use in the BE HEARD trials was low (see section B.2.3.3). However, there was a relatively high level of systemic antibiotic use during the BE HEARD trials, the majority of which was not rescue medication for HS (see section B.2.4.6). This means that the strict prespecified intercurrent event definition may not reflect bimekizumab use in clinical practice, as patients would not be expected to discontinue therapy for HS after the use of antibiotics. In addition, the prespecified definition complicates indirect comparisons with secukinumab using data from the phase 3 trials SUNSHINE and SUNRISE, in which non-

response was imputed following the use of systemic antibiotics for HS specifically (HS-ABX) [48].

Accordingly, a *post hoc* analysis of the BE HEARD trial results was conducted in which intercurrent events were defined as discontinuation due to lack of efficacy, discontinuation due to adverse events or use of antibiotics deemed by the principal investigator to be rescue medication for HS.

Analyses included in submission

Results are presented for the individual BE HEARD trials for endpoints listed in the statistical testing hierarchy (see section B.2.4.4). For other endpoints, data are shown for the pooled BE HEARD trial populations (see section B.2.6.1).

Results for the primary and key secondary endpoints are presented in the main submission using the *post hoc* analysis of the individual BE HEARD trials. Results for exploratory endpoints are shown using the *post hoc* analysis of data from the pooled BE HEARD trial population (see section B.2.6.1). For binary outcomes, results are also presented using OC data, allowing for comparison with the maintenance phase analyses in the secukinumab SUNSHINE and SUNRISE trials (discussed in Appendix D.1.4.5) and as some mNRI for HS-ABX models failed to converge (see section B.2.6.1).

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Methodology

B.2.3.1.1 Study design and interventions

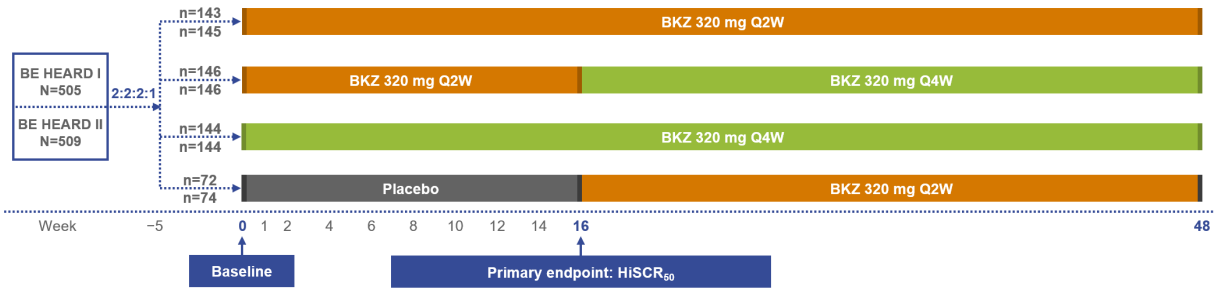
BE HEARD I and BE HEARD II

BE HEARD I (NCT04242446) and BE HEARD II (NCT04242498) are two identically designed, randomised, placebo-controlled, double-blind, multicentre phase 3 trials [1, 2]. The objective of these trials was to evaluate the efficacy and safety of bimekizumab in patients with moderate to severe HS. The study populations comprised adult patients (aged at least 18 years) with a diagnosis of moderate to severe HS for at least 6 months and a history of inadequate response to systemic antibiotics for treating HS.

The BE HEARD trials included a 16-week initial treatment period and a 32-week maintenance period. Patients were randomised 2:2:2:1 to bimekizumab 320 mg every 2 weeks (Q2W), bimekizumab 320 mg every 4 weeks (Q4W), bimekizumab 320 mg Q2W initial treatment followed by bimekizumab 320 mg Q4W maintenance treatment, or placebo followed by bimekizumab 320 mg Q2W maintenance treatment (Figure 4).

Results for all BE HEARD treatment groups are presented in this submission, but the focus of the economic model presented in section B.3 is bimekizumab 320 mg Q2W initial treatment followed by bimekizumab 320 mg Q4W (hereafter bimekizumab 320 mg Q2W/Q4W).

Figure 4 BE HEARD I and II study design



BKZ, bimekizumab; HiSCR, hidradenitis suppurativa clinical response; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks. Source: Kimball *et al.* 2023, AAD presentation [115].

BE HEARD EXT

Following completion of the BE HEARD I and BE HEARD II trials, patients were eligible to transfer to the BE HEARD EXT long-term open-label extension study, in which they were assigned to receive bimekizumab 320 mg Q2W or Q4W, according to their HiSCR90 response status (see section B.2.3.1.6) calculated using the average lesion count from weeks 36, 40 and 44 in BE HEARD I and BE HEARD II [118]:

- HiSCR90 response: received bimekizumab 320 mg Q4W in BE HEARD EXT
- No HiSCR90 response: received bimekizumab 320 mg Q2W in BE HEARD EXT

If a participant in the bimekizumab 320mg Q4W group did not have a HiSCR90 response over a consecutive 8-week period on average (three study visits), or if they had less than a HiSCR75 response at any single visit, the investigator in consultation with the participant could increase the bimekizumab dose to 320 mg Q2W [118].

B.2.3.1.2 Randomisation and blinding

Patients were randomised using an interactive response system, with stratification by Hurley stage (II or III) and baseline antibiotic use [1, 2]. Patients and investigators were unaware of the treatment received by each patient. Because of differences in appearances between bimekizumab and placebo, injections were administered at the investigational sites by unblinded, dedicated study personnel. Unblinded personnel were not involved in the study in any other way [1, 2].

B.2.3.1.3 Eligibility criteria

Inclusion and exclusion criteria are summarised in Table 8. Patients were required to have a diagnosis of moderate to severe HS; HS lesions in ≥2 distinct anatomic areas; and ≥ 5 inflammatory lesions (abscess and inflammatory nodule [AN] count) at screening and baseline. Patients with > 20 DTs at baseline were excluded.

B.2.3.1.4 Concomitant medication

Antibiotic use at study entry was permitted if a patient received a stable dose and regimen of doxycycline, minocycline, or an equivalent systemic tetracycline, and if the antibiotic was already in use for 28 days prior to trial baseline visit [1, 2]. The dose and regimen were expected to remain stable throughout study participation, but at least through week 16 (patients who interrupted their stable dose of antibiotic during the study and subsequently restarted the same tetracycline antibiotic were not considered to have received rescue medication) [1, 2].

Concomitant use of wound care dressings on HS wounds was allowed; however, options were limited to alginates, hydrocolloids, and hydrogels. Concomitant use of saline, water, and/or Vaseline (petroleum jelly) was allowed for care of skin lesions [1, 2].

Opioid analgesics were not permitted for any indication. Stable doses of non-opioid analgesics for HS-related pain or other medical conditions were permitted. For worsening HS-related pain after baseline, ibuprofen or paracetamol use was permitted [1, 2].

Prohibited medications are shown in Appendix D.2, Table 114.

Table 8 Key eligibility criteria in BE HEARD I and II

Inclusion criteria	Exclusion criteria
≥ 18 years of age. Diagnosis of moderate to severe HS at least 6 months prior to the baseline visit. HS lesions in ≥2 distinct anatomic areas, one of which must be at least Hurley stage II/III at screening and baseline. Moderate to severe HS, defined as ≥ 5 inflammatory lesions (AN count) at screening and baseline. History of inadequate response to systemic antibiotics for treating HS at screening. For female participants: not pregnant; not breastfeeding; not a woman of childbearing potential, unless agreeing to follow contraceptive guidance during treatment period and for at least 20 weeks after last dose of IMP. Non-biological systemic therapies had to have been discontinued ≥ 4 weeks before the baseline visit (except for permitted, stable doses of antibiotics). Biological therapies had to have been discontinued ≥ 12 weeks, ≥ 6 months or ≥ 5 half-lives prior to the baseline visit, depending on therapy (see Appendix D.2, Table 114).	> 20 DTs at baseline Any medical or psychiatric condition that could compromise the participant's ability to participate in the study: Immunosuppressive condition/other active skin disease or condition (e.g., bacterial cellulitis, candida intertrigo, extensive condyloma). Diagnosis of sarcoidosis, systemic lupus erythematosus, or active IBD. Note: study participants with a diagnosis of Crohn's disease or ulcerative colitis were allowed if they had no active symptomatic disease at screening or baseline. Active infection or history of infections, latent/active TB, high risk of TB exposure or current pulmonary nontuberculous mycobacterial infection. Hepatitis B, hepatitis C or human immunodeficiency infection. Concurrent malignancy. History of lymphoproliferative disease. Presence of moderately severe/severe major depression, or active suicidal ideation or positive suicide behaviour. Laboratory abnormalities at screening.

AN: abscess and inflammatory nodule; DT, draining tunnel; HS, hidradenitis suppurativa; IBD: inflammatory bowel disease; IMP: investigational medicinal product; TB: tuberculosis.

Source: BE HEARD CSRs [1, 2], Kimball *et al.* 2023, AAD presentation [115].

B.2.3.1.5 Settings and locations

BE HEARD I was conducted at 88 sites in North America, Europe, Australia, Israel and Turkey [113]. BE HEARD II was conducted at 93 sites in North America, Europe, Australia, Israel and Japan [114]. A total of four sites in the UK (Leeds, London, Newcastle-upon-Tyne and Northampton; five UK patients in total) participated in the BE HEARD II trial [114].

B.2.3.1.6 Study endpoints and outcome measures

The primary endpoint of the BE HEARD trials was the proportion of patients with a HiSCR50 response, defined as a ≥ 50% reduction from baseline in total AN count, with no increase from baseline in abscess or DT count, at week 16. HiSCR50 is a validated HS endpoint which reflects a clinically meaningful response to treatment [15].

The key ranked secondary endpoints of the BE HEARD trials, all assessed at week 16, were:

- The proportion of patients with HiSCR75.
- The proportion of patients with flare (BE HEARD II only).
- Absolute change from baseline in DLQI total score.
- Absolute change from baseline in the worst HS skin pain score at week 16, as assessed by the “worst pain” item (11-point numerical rating scale) in the Hidradenitis Suppurativa Symptom Daily Diary (HSSDD)
- Skin pain response based on the threshold for clinically meaningful change (defined as at least a 3-point decrease from baseline in HSSDD weekly worst skin pain score) at week 16 among study participants with a score of ≥ 3 at baseline

Outcome measures assessed in the BE HEARD trials and described in this submission are shown in Table 9.

Table 9 Summary of BE HEARD trial outcome measures presented in this submission

Outcome	Definition
HiSCR25, HiSCR50, HiSCR75, HiSCR90, HiSCR100	Patients achieving a 50% reduction from baseline in the total AN count, with no increase from baseline in abscess or DT count are defined as HiSCR50 responders [15, 142]. HiSCR50 is a validated HS endpoint which demonstrates a clinically meaningful response [15, 142]. Other HiSCR thresholds reported in this submission are HiSCR25, HiSCR75, HiSCR90 and HiSCR100 (25%, 75%, 90% and 100% reduction from baseline, respectively, in total AN count, with no increase from baseline in abscess or DT count).
AN lesion count AN50	Absolute numbers of abscesses and inflammatory nodules. Abscesses are red, sore bumps that often get larger, break open, and ooze pus. Nodules are small bumps or lumps under the skin that can become larger and inflamed over time.

Outcome	Definition
	AN50 is defined as a 50% reduction in abscess and inflammatory nodule count
DT count	Absolute numbers of draining tunnels. Draining tunnels (also termed sinus tracts or fistulas) are narrow tunnels under the skin that are open on one end and let fluid escape or drain fluid.
IHS4, IHS4-55	The IHS4 is a validated tool to dynamically assess HS severity [17]. The IHS4 score is calculated as 1 x the number of nodules plus 2 x the number of abscesses plus 4 x the number of DTs. Scores ≤ 3 indicate mild HS, 4–10 moderate HS, and ≥ 11 severe HS [17]. A 55% reduction in IHS4 total score is used as a dichotomous outcome measure (IHS4-55) [16, 18, 19].
Flare	A disease flare was defined as at least a 25% increase in AN count with an absolute increase of ≥2 AN relative to baseline.
HSSDD symptoms	The HSSDD is an HS-specific daily symptom diary (data are collected daily and analysed as weekly averages) [143]. The HSSDD assesses skin pain (see below), itch, smell/odour and drainage/oozing [143].
Pain	Absolute change from baseline in Skin Pain score was assessed using the "worst skin pain" item (11-point NRS) in the HSSDD. Skin pain response was based on the threshold for clinically meaningful change (defined as at least a 3-point decrease from baseline in HSSDD weekly worst skin pain score) among study participants with a score of ≥ 3 at baseline. An alternative definition of skin pain response, NRS30 (a ≥ 30% reduction and reduction of ≥ 2 units from baseline in Worst Skin Pain HSSDD of Skin Pain, assessed in patients with a baseline HSSDD score of ≥ 3) was also explored. Pain responses according to the HSSQ were also investigated, with a response defined as a score of 0 among patients with baseline scores ≥ 1.
HiSQOL	The HiSQOL is a validated 17-item HS-specific questionnaire to assess study participants' HRQoL. The HiSQOL includes three subscales: symptoms, psychosocial, and activities and adaptations [144].
DLQI	The DLQI comprises ten questions based on skin disease symptoms and impact on HRQoL [145]. Scores range from 0 to 30, with higher scores indicating worse HRQoL [145]. A 4 point improvement is defined as an MCID among patients with baseline scores ≥ 4 [146].
EQ-5D-3L	The EQ-5D is a standardised instrument developed by the EuroQoL Group for use as a generic, preference-based measure of health outcome. The EQ-5D questionnaire is used to calculate a utility score based on a descriptive profile, or 'health state'. Data in the BE HEARD trials were collected using the 3-level version (EQ-5D-3L).

AN, abscess and inflammatory nodule; DLQI, Dermatology Life Quality Index; DT, draining tunnel; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; HiSCR, hidradenitis suppurativa clinical response; HiSQOL, Hidradenitis Suppurativa Quality of Life; HRQoL, health-related quality of life; HS, hidradenitis suppurativa; HSSDD, Hidradenitis Suppurativa Symptom Diary; HSSQ, Hidradenitis Suppurativa Symptom Questionnaire; IHS4, International Hidradenitis Suppurativa Severity Score System; MCID, minimal clinically important difference; NMA, network meta-analysis; NRS, numerical rating scale.

B.2.3.2 Comparative summary of trial methodology

Table 10 Comparative summary of trial methodology

Trial number (acronym)	BE HEARD I (NCT04242446) and BE HEARD II (NCT04242498) [1, 2, 113, 114]	
Location	BE HEARD I, 88 sites in North America, Europe, Australia, Israel and Turkey BE HEARD II, 93 sites in North America, Europe, Australia, Israel and Japan.	
Trial design	Randomised, placebo-controlled, double-blind, multicentre phase 3 trials with a 16-week initial treatment period and a 32-week maintenance period	
Eligibility criteria for participants	Adult patients with a diagnosis of HS with ≥ 5 inflammatory lesions (AN) at least 6 months prior to baseline HS lesions present in at least 2 distinct anatomic areas, one of which is at least Hurley stage II Moderate to severe HS defined as a total of ≥ 5 inflammatory lesions History of inadequate response to a course of a systemic antibiotics for treatment of HS Patients with > 20 DTs were excluded	
Settings and locations where the data were collected	Data were collected during scheduled visits to study centres (daily diaries [HSSDD] were completed by patients only up to week 16)	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	2:2:2:1 to bimekizumab 320 mg every 2 weeks (Q2W), bimekizumab 320 mg every 4 weeks (Q4W), bimekizumab 320 mg Q2W initial treatment followed by bimekizumab 320 mg Q4W maintenance treatment (Q2W/Q4W), or placebo followed by bimekizumab 320 mg Q2W maintenance treatment	
Permitted and disallowed concomitant medication	BE HEARD I: Bimekizumab 320 mg Q2W, n = 143 Q4W, n = 144 Q2W/Q4W, n = 146 Placebo/bimekizumab 320 mg Q2W, n = 72	BE HEARD II: Bimekizumab 320 mg Q2W, n = 145 Q4W, n = 144 Q2W/Q4W, n = 146 Placebo/bimekizumab 320 mg Q2W, n = 74
Primary outcomes (including scoring methods and timings of assessments)	Proportion of patients with HiSCR50 at week 16	
Other outcomes used in the economic model	HiSCR25, HiSCR75, HiSCR90, EQ-5D, AEs (sensitivity analysis only)	
Pre-planned subgroups	Pre-planned subgroups described in submission: previous biologic experience (yes / no); weight (≤ 100 kg / > 100 kg); Hurley stage at baseline (II / III); sex (female / male); race (black/other races)	

AE, adverse event; AN, abscess and inflammatory nodule; DT, draining tunnel; HS, hidradenitis suppurativa; HiSCR, hidradenitis suppurativa clinical response; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary.
Sources: clinicaltrials.gov [113, 114]; Kimball 2023 [115]; BE HEARD CSRs [1, 2].

B.2.3.3 Baseline characteristics

Demographics and baseline characteristics of patients included in the BE HEARD studies are shown in Table 11 [1, 2]. In both studies, baseline characteristics were broadly balanced across the treatment groups. In BE HEARD I, there were more female patients and patients weighing > 100 kg in the bimekizumab 320 mg Q4W arm than in the other arms. Although balanced between individual study arms, BE HEARD II included fewer female patients, fewer patients with Hurley stage III HS, and fewer patients with a history of biologic use, compared with BE HEARD I.

At baseline, antibiotic use was low, with 8% of patients in BE HEARD I and 9% of patients in BE HEARD II on stable, permitted antibiotic regimens [1, 2].

Across all randomised groups, 24.8% of participants in BE HEARD I and 13.0% of participants in BE HEARD II had previously used biological therapies (all prior biologic treatments received by patients were for HS) [126, 127]. The most frequent prior biologic was adalimumab (BE HEARD I, 22.4% of participants; BE HEARD II, 12.3% of participants). The corresponding proportions of patients in BE HEARD I and BE HEARD II who had used other biologics were: infliximab, 5.2% and 1.8%; guselkumab, 2.0% and 0.6%; other biologics, < 1% in each trial [124, 125].

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis population

Efficacy analyses were conducted using the randomised set (RS), which included all patients randomised to treatment [1, 2]. Some efficacy endpoint analyses specific to the maintenance treatment period used the maintenance set (MS), which consisted of all study participants who received at least one dose (full or partial) of bimekizumab in the maintenance treatment period [1, 2].

Safety analyses were conducted using the safety set (SS), which included all study participants who received at least one dose (full or partial) of investigational product, and the active medication set (AMS), defined as all study participants who had received at least one dose (full or partial) of bimekizumab [1, 2].

Analyses of BE HEARD EXT were conducted using the open-label extension (OLE) set, which included all patients who received at least one dose of bimekizumab in BE HEARD EXT.

Table 11 Demographics and baseline characteristics in BE HEARD I and II

Category	BE HEARD I				BE HEARD II			
	Placebo n = 72	BKZ 320 mg Q4W n = 144	BKZ 320 mg Q2W n = 289	All Participants N = 505	Placebo n = 74	BKZ 320 mg Q4W n = 144	BKZ 320 mg Q2W n = 291	All Participants N = 509
Study participant characteristics								
Age, years, mean ± SD	36.4 ± 12.4	36.3 ± 11.2	36.9 ± 12.4	36.7 ± 12.0	38.1 ± 13.2	35.2 ± 11.9	36.9 ± 12.3	36.6 ± 12.4
Gender, n(%)								
Male	28 (38.9)	46 (31.9)	113 (39.1)	187 (37.0)	43 (58.1)	67 (46.5)	141 (48.5)	251 (49.3)
Female	44 (61.1)	98 (68.1)	176 (60.9)	318 (63.0)	31 (41.9)	77 (53.5)	150 (51.5)	258 (50.7)
Body weight, kg, mean ± SD	94.62 ± 24.81	102.68 ± 24.71	97.23 ± 25.36	98.42 ± 25.21	100.28 ± 23.65	95.29 ± 21.99	95.41 ± 24.22	96.09 ± 23.55
≤ 100 kg, n (%)	48 (66.7)	67 (46.5)	168 (58.1)	283 (56.0)	41 (55.4)	86 (59.7)	192 (66.0)	319 (62.7)
> 100 kg, n (%)	24 (33.3)	77 (53.5)	118 (40.8)	219 (43.4)	33 (44.6)	57 (39.6)	99 (34.0)	189 (37.1)
BMI, kg/m^2, mean ± SD	32.36 ± 7.77	35.35 ± 8.06	33.36 ± 8.31	33.79 ± 8.22	33.81 ± 8.70	32.24 ± 7.46	32.01 ± 8.04	32.34 ± 7.99
Smoking status, n (%)								
Never	27 (37.5)	62 (43.1)	111 (38.4)	200 (39.6)	26 (35.1)	57 (39.6)	106 (36.4)	189 (37.1)
Current	37 (51.4)	53 (36.8)	127 (43.9)	217 (43.0)	38 (51.4)	73 (50.7)	134 (46.0)	245 (48.1)
Former	7 (9.7)	28 (19.4)	43 (14.9)	78 (15.4)	10 (13.5)	14 (9.7)	49 (16.8)	73 (14.3)
Racial group, n (%)								
White	55 (76.4)	105 (72.9)	233 (80.6)	393 (77.8)	64 (86.5)	119 (82.6)	232 (79.7)	415 (81.5)
Black	8 (11.1)	21 (14.6)	41 (14.2)	70 (13.9)	5 (6.8)	13 (9.0)	22 (7.6)	40 (7.9)
Asian [a]	3 (4.2)	3 (2.1)	2 (0.7)	8 (1.6)	5 (6.8)	7 (4.9)	22 (7.6)	34 (6.7)
Geographical region, n (%)								
North America	28 (38.9)	76 (52.8)	132 (45.7)	236 (46.7)	26 (35.1)	45 (31.3)	78 (26.8)	149 (29.3)
Central/Eastern Europe	5 (6.9)	10 (6.9)	30 (10.4)	45 (8.9)	28 (37.8)	64 (44.4)	123 (42.3)	215 (42.2)
Western Europe	33 (45.8)	49 (34.0)	100 (34.6)	182 (36.0)	15 (20.3)	28 (19.4)	68 (23.4)	111 (21.8)
Asia/Australia	6 (8.3)	9 (6.3)	27 (9.3)	42 (8.3)	5 (6.8)	7 (4.9)	22 (7.6)	34 (6.7)
Baseline disease characteristics								
Duration of disease, years, Mean ± SD	11.51 ± 9.87	8.77 ± 8.50	8.51 ± 7.62	9.01 ± 8.28	8.03 ± 8.61	5.77 ± 5.38	7.35 ± 7.38	7.00 ± 7.11
Hurley stage (derived), n (%) [b]								
II	34 (47.2)	71 (49.3)	149 (51.6)	254 (50.3)	45 (60.8)	89 (61.8)	177 (60.8)	311 (61.1)
III	38 (52.8)	73 (50.7)	140 (48.4)	251 (49.7)	29 (39.2)	55 (38.2)	114 (39.2)	198 (38.9)
AN count, mean ± SD	15.0 ± 11.9	17.8 ± 25.3	15.3 ± 13.5	16.0 ± 17.5	13.9 ± 7.8	17.6 ± 15.4	16.7 ± 15.5	16.5 ± 14.6

Category	BE HEARD I				BE HEARD II			
	Placebo n = 72	BKZ 320 mg Q4W n = 144	BKZ 320 mg Q2W n = 289	All Participants N = 505	Placebo n = 74	BKZ 320 mg Q4W n = 144	BKZ 320 mg Q2W n = 291	All Participants N = 509
Hurley stage II [c]	13.4 ± 10.5	16.0 ± 32.5	12.1 ± 10.9	13.3 ± 19.5	12.8 ± 8.1	15.5 ± 13.0	13.0 ± 9.3	13.7 ± 10.3
Hurley stage III [c]	16.5 ± 13.0	19.6 ± 15.3	18.8 ± 15.1	18.7 ± 14.8	15.5 ± 7.2	21.0 ± 18.3	22.3 ± 20.7	21.0 ± 18.7
DT count, mean ± SD	3.2 ± 4.0	3.8 ± 4.9	4.0 ± 4.9	3.8 ± 4.8	3.5 ± 3.7	2.8 ± 3.1	3.6 ± 4.0	3.4 ± 3.7
Hurley stage II [c]	1.5 ± 2.1	0.9 ± 1.4	1.6 ± 2.2	1.4 ± 2.0	2.0 ± 2.1	2.1 ± 2.4	2.1 ± 2.2	2.1 ± 2.3
Hurley stage III [c]	4.7 ± 4.7	6.7 ± 5.4	6.6 ± 5.5	6.3 ± 5.4	5.8 ± 4.5	3.9 ± 3.7	5.9 ± 4.9	5.3 ± 4.6
IHS4 score, mean ± SD	30.8 ± 24.3	37.7 ± 40.6	35.0 ± 30.4	35.2 ± 32.9	30.4 ± 19.2	32.3 ± 25.7	34.4 ± 29.7	33.2 ± 27.3
HiSQOL total score, mean ± SD	25.89 ± 14.82	28.24 ± 14.35	25.06 ± 12.95	26.10 ± 13.69	26.92 ± 13.44	23.29 ± 13.06	24.22 ± 12.85	24.35 ± 13.02
Symptom score	8.35 ± 3.81	8.38 ± 3.70	8.03 ± 3.38	8.18 ± 3.54	8.04 ± 3.59	7.38 ± 3.34	7.69 ± 3.36	7.65 ± 3.39
Psychosocial score	6.21 ± 5.41	6.78 ± 5.04	5.78 ± 4.58	6.13 ± 4.85	6.27 ± 5.09	4.97 ± 4.56	5.24 ± 4.74	5.32 ± 4.75
Activities and adaptations score	11.32 ± 7.66	13.08 ± 7.63	11.25 ± 6.89	11.79 ± 7.26	12.60 ± 7.43	10.94 ± 7.13	11.29 ± 6.81	11.38 ± 7.00
DLQI total score, mean ± SD	12.4 ± 8.0	12.8 ± 7.6	11.5 ± 6.6	12.0 ± 7.1	11.9 ± 6.1	10.5 ± 7.0	10.6 ± 6.5	10.8 ± 6.6
HSSDD worst pain score, mean ± SD	5.96 ± 2.47	5.94 ± 2.58	5.49 ± 2.54	5.68 ± 2.55	4.96 ± 2.44	5.33 ± 2.48	5.33 ± 2.41	5.28 ± 2.43
Antibiotic use (derived), n (%) [d]								
Yes	5 (6.9)	8 (5.6)	27 (9.3)	40 (7.9)	6 (8.1)	10 (6.9)	30 (10.3)	46 (9.0)
No	67 (93.1)	136 (94.4)	262 (90.7)	465 (92.1)	68 (91.9)	134 (93.1)	261 (89.7)	463 (91.0)
Prior biologic use for HS, n (%) [e]								
Yes	19 (26.4%)	31 (21.5%)	75 (26.0%)	125 (24.8%)	10 (13.5%)	16 (11.1%)	40 (13.7%)	66 (13.0%)
No	53 (73.6%)	113 (78.5%)	214 (74.0%)	380 (75.2%)	64 (86.5%)	128 (88.9%)	251 (86.3%)	443 (87.0%)

[a] BE HEARD II included 28 Japanese participants. [b] Derived Hurley stage for each participant was the worst overall Hurley stage derived from the Hurley Stages recorded across all anatomical regions. [c] Derived Hurley stage. [d] Derived antibiotic use at baseline was defined as eCRF record of a stable dose and regimen of systemic tetracycline use for at least 28 days prior to baseline; otherwise, derived antibiotic use at baseline was defined as "No". [e] All prior biologic treatments received by patients were for HS; two patients initially included in the 'prior biologic use' subgroup were switched to the 'biologic-naive' subgroup, as they had not received true biologic therapy.

AN, abscess and inflammatory nodule; BKZ, bimekizumab; BMI, body mass index; DLQI: Dermatology Life Quality Index; HiSQOL: Hidradenitis Suppurativa Quality of Life; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary; IHS4, International Hidradenitis Suppurativa Severity Score System; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set; SD; standard deviation; TNFi, tumour necrosis factor inhibitor.

Sources: BE HEARD CSRs [1, 2]; BE HEARD baseline characteristics tables [126, 127].

B.2.4.2 Management of dropouts and missing data

The management of dropouts, missing data and intercurrent events (defined as in section B.2.4.2) is shown in Table 12 [1, 2].

Table 12 Management of dropouts, missing data and intercurrent events in the BE HEARD trials

Missing data method	Definition
Continuous endpoints	
Multiple imputation (MI)	Intermittent missing data were imputed using MI with the MCMC method. Monotone missing data were imputed using MI with the monotone regression method. Participants who experienced an intercurrent event were treated as missing at all subsequent visits and imputed using the MI method for missing data.
Binary endpoints	
Modified non-responder imputation (mNRI)	For binary endpoints based on continuous measures (e.g. HiSCR outcomes), missing data, including missing data following discontinuation for reasons other than lack of efficacy or AEs, were imputed using MI, and dichotomised to obtain the response status. Participants who experienced an intercurrent event were treated as non-responders at all subsequent visits.
Observed case (OC)	Data were analysed as observed. Missing data and intercurrent events (including antibiotic use) were not considered.

HiSCR, hidradenitis suppurativa clinical response; MCMC, Markov chain Monte Carlo imputation; MI, multiple imputation; mNRI, modified non-responder imputation; OC, observed case.

B.2.4.3 Intercurrent events and non-responder imputation

Non-responder imputation was conducted using both prespecified and alternative criteria for an intercurrent event (Table 13). Discontinuation due to lack of efficacy or AEs was considered an intercurrent event under both definitions.

In the prespecified definition based on the trial protocol, participants who received a systemic antibiotic for any reason (all-ABX) during the study period were deemed to have experienced an intercurrent event and to be non-responders for all future assessment timepoints for binary endpoints; when combined with MI for other missing data this is the mNRI for all-ABX analysis approach used for the results reported in Appendix D.4.

In the alternative definition applied in the *post hoc* analysis, participants who received a systemic antibiotic defined as HS rescue treatment, as determined by the principal investigator (HS-ABX) during the study period were deemed to have experienced an intercurrent event. For binary endpoints, there were labelled as non-responders for all future assessment timepoints; when combined with MI for other missing data this is the mNRI for HS-ABX analysis approach used for the results reported in the main body of this submission. The HS-ABX definition of intercurrent events is similar to the definition used in the SUNSHINE and SUNRISE trials of secukinumab [48]. Accordingly, the use of this definition

to analyse the BE HEARD trial data is necessary to allow like-for-like comparisons between the bimekizumab and secukinumab phase 3 trials.

For continuous endpoints, patients who experienced an intercurrent event were labelled as missing for all subsequent visits and their missing values were imputed using MI (see section B.2.4.2) [1, 2].

As described in section B.2.2, the *post hoc* analysis (HS-ABX) is used for the results presented in the main submission; data using the prespecified criteria are shown in Appendix D.4.

Table 13 Criteria for intercurrent events

Prespecified criteria (BE HEARD trial protocols)	Alternative criteria (post hoc analysis)
Discontinuation due to lack of efficacy	
Discontinuation due to AE	
Use of any systemic antibiotic that was newly initiated on or after baseline visit (All-ABX) [a]	Use of any systemic antibiotic defined as HS rescue treatment, as determined by the principal investigator, that was newly initiated on or after baseline visit (HS-ABX) [a]

ABX, antibiotics; AE, adverse event; HS, hidradenitis suppurativa.

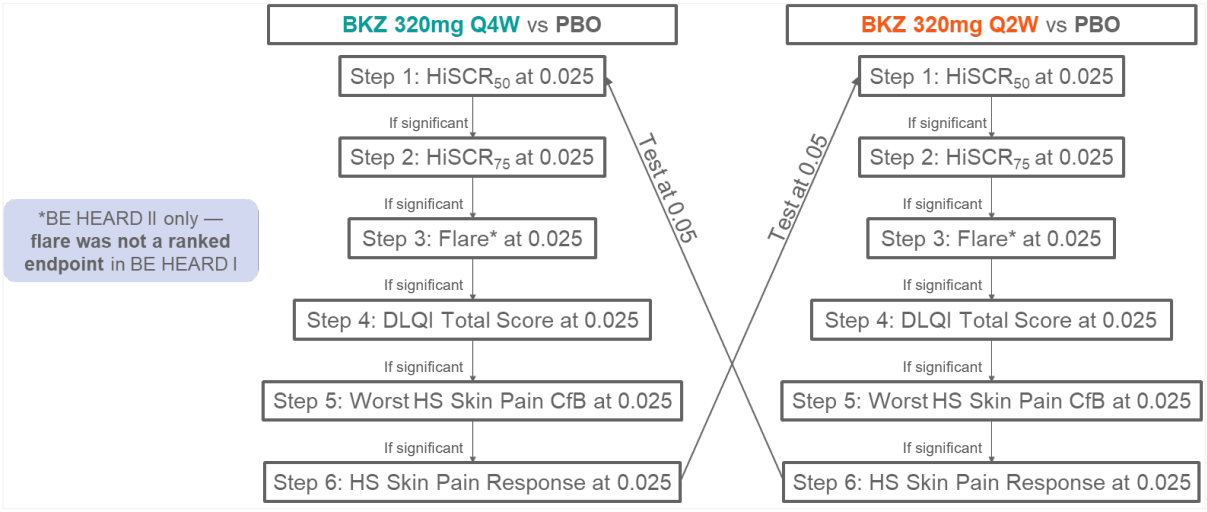
[a] Antibiotic use was permitted if a stable dose and regimen of doxycycline, minocycline, or an equivalent systemic tetracycline, and if already in use for 28 days prior to baseline (see section B.2.3.1.4).

B.2.4.4 Statistical testing procedure

For each trial, a hierarchical statistical testing procedure was conducted as described below. This sequential testing controls for multiple comparisons in the primary/secondary endpoints.

- Each bimekizumab dose of 320mg Q2W and 320mg Q4W was compared with placebo in the first instance at a significance level of 0.025 in a stepwise manner as shown in Figure 5.
- In the event that all steps were significant at 0.025 for a given dose, all steps were to be repeated for the other dose using a significance level of 0.05.
- If all steps for a given dose were significant at 0.025, then 97.5% confidence intervals (CIs) were to be reported for that arm and 95% CIs for the opposite arm.
- If both arms were significant on all endpoints at 0.025, then 95% CIs were to be reported for both arms.
- If both arms feature an endpoint where they are not significant at 0.025, 97.5% CIs were to be reported for all outcomes.

Figure 5 Statistical testing procedure in BE HEARD I and BE HEARD II



BKZ, bimekizumab; CfB, change from baseline; CI, confidence interval; DLQI, dermatology life quality index; DT, draining tunnel; HiSCR, hidradenitis suppurativa clinical response; $HiSCR_{50/75}$, ≥50/75% reduction from baseline in the total AN count with no increase from baseline in abscess or DT count; HS, hidradenitis suppurativa; PBO, placebo; Q2W, every two weeks; Q4W, every four weeks

With a 2-sided significance level of 0.025, for both trials the sample size provided 73% power for detecting at least a difference of 1.5 (bimekizumab Q4W vs placebo) for the worst skin pain change from baseline endpoint.

B.2.4.5 Participant flow

Full details of patient disposition in the phase 3 studies are shown in Appendix D.3, Figure 41, Figure 42, Figure 43 and Figure 44.

In BE HEARD I, 505 participants were randomised, 451 (89.3%) completed the initial treatment period and 333 (74.3%) completed the maintenance treatment period [1]. In BE HEARD II, 509 participants were randomised, 464 (91.2%) completed the initial treatment period and 387 (83.6%) completed the maintenance treatment period [2]. In both trials the most common reasons for discontinuation were withdrawal of consent and AEs [1, 2].

B.2.4.6 Protocol deviations and systemic antibiotic use

In the initial treatment period, most study participants had no important protocol deviations (BE HEARD I, 410/505 patients [81.2%]; BE HEARD II, 427/509 [83.9%]). Most of the reported important protocol deviations were prohibited concomitant medication use (BE HEARD I, 77/95 patients; BE HEARD II, 62/82 patients) [1, 2].

There were few important protocol deviations in the maintenance treatment period (BE HEARD I, 8/448 patients; BE HEARD II, 32/463 patients). The most common protocol deviation was prohibited concomitant medication use (BE HEARD I, 6/8 patients; BE HEARD II, 13/32 patients) [1, 2].

Systemic antibiotic use in the BE HEARD trials is shown in Table 14. During both the initial treatment period and the maintenance treatment period, the majority of systemic antibiotic use was not considered by the study investigators to be rescue medication for HS [1, 2]. The proportion of patients who did receive antibiotics as HS rescue medication was generally similar across arms.

Because a substantial number of patients received systemic antibiotics for reasons other than HS, and to better align with the real-world use of antibiotics to treat HS disease-specific issues, which include the use of evidence-based antibiotics specified in treatment guidelines for HS, a *post hoc* analysis was conducted in which use of antibiotics for reasons other than HS was not considered as an intercurrent event and was not imputed as non-response (see section B.2.4.2).

Table 14 Initiation of systemic antibiotic rescue therapy in BE HEARD trials

	BE HEARD I				BE HEARD II			
	BKZ 320 mg Q2W/ Q2W	BKZ 320 mg Q2W/ Q4W	BKZ 320 mg Q4W/ Q4W	PBO/ BKZ 320 mg Q2W	BKZ 320 mg Q2W/ Q2W	BKZ 320 mg Q2W/ Q4W	BKZ 320 mg Q4W/ Q4W	PBO/ BKZ 320 mg Q2W
Initial treatment period								
All-ABX	47/289 (16.3%)		22/144 (15.3%)	15/72 (20.8%)	45/291 (15.5%)		18/144 (12.5%)	6/74 (8.1%)
HS-ABX	12/289 (4.2%)		2/144 (1.4%)	4/72 (5.6%)	14/291 (4.8%)		7/144 (4.9%)	4/74 (5.4%)
Maintenance treatment period								
All-ABX	49/129 (38.0%)	44/129 (34.1%)	49/125 (39.2%)	30/65 (46.2%)	37/131 (28.2%)	42/130 (32.3%)	32/133 (24.1%)	15/69 (21.7%)
HS-ABX	9.3%	10.1%	14.4%	18.5%	6.1%	10.0%	11.3%	8.7%

Percentages are the proportion of patients in each treatment arm (with pooled bimekizumab Q2W arms during the initial treatment period) who received any systemic antibiotic or antibiotics as HS rescue medication.
All-ABX, all systemic antibiotic therapy; HS-ABX, systemic antibiotic use considered by the investigator to be rescue medication for HS.
ABX, antibiotics; BKZ, bimekizumab; HS, hidradenitis suppurativa; PBO, placebo.
Source: BE HEARD CSRs [1, 2]; BE HEARD data tables [119, 120].

B.2.4.7 Concomitant rescue interventions

The incidence of concomitant rescue interventions during the initial treatment period is shown in Table 15 [141]. Over 16 weeks, the proportion of patients requiring concomitant rescue interventions for HS was numerically lower among patients treated with bimekizumab Q2W or Q4W than among those receiving placebo [141].

Table 15 Concomitant rescue interventions during initial treatment period in pooled BE HEARD trial population (RS)

Proportion of patients with intervention, n (%)	Bimekizumab 320 mg Q2W (n = 580)	Bimekizumab 320 mg Q4W (n = 288)	Placebo (n = 146)
Any rescue intervention	50 (8.6%)	31 (10.8%)	22 (15.1%)
≥ 1 medical intervention	44 (7.6%)	19 (6.6%)	18 (12.3%)
≥ 1 rescue analgesic	24 (4.1%)	12 (4.2%)	13 (8.9%)
≥ 1 rescue systemic antibiotic	26 (4.5%)	9 (3.1%)	8 (5.5%)
≥ procedural intervention	15 (2.6%)	16 (5.6%)	8 (5.5%)
≥ 1 incision and drainage intervention	10 (1.7%)	8 (2.8%)	5 (3.4%)
≥ 1 intralesional triamcinolone injection	6 (1.0%)	8 (2.8%)	5 (3.4%)

Q2W, every 2 weeks; Q4W, every 4 weeks.
Source: Bechara 2024, AAD presentation [141].

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality assessment for the BE HEARD trials is shown in Table 16, with a detailed description of the quality assessment presented in Appendix D.4, Table 115.

Table 16 Critical appraisal of BE HEARD trials

Trial	BE HEARD I and BE HEARD II
Bias arising from the randomisation process	Low
Bias due to deviations from intended interventions	Low
Bias due to missing outcome data	Low
Bias in measurement of the outcome	Low
Bias in selection of the reported result	Low
Overall bias	Low

Critical appraisal was conducted in October 2023 using the Cochrane Risk of Bias tool (RoB 2) [147] as part of the SLR of clinical evidence described in Appendix D.
Sources: Kimball *et al.* 2023, AAD presentation [115]; Zouboulis *et al.* 2023 [129]; BE HEARD CSRs [1, 2].

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 Summary of presented analyses

As described in sections B.2.2 and B.2.4.3, data from the BE HEARD trials were analysed using two different definitions of intercurrent events relating to antibiotic use. In addition, for multiple endpoints, analyses have been conducted using data for the pooled population of the two trials (most publicly available BE HEARD data are pooled). Further, for the primary and key secondary endpoints at week 16, all patients receiving initial treatment with bimekizumab 320 mg Q2W were analysed as one group – these data are reported for the individual BE HEARD trials for consistency with the prespecified statistical analysis methods

and with the NMA described in section B.2.9, which is based on individual trial data. From week 16, results are reported by randomised treatment sequence, with initial and maintenance treatment doses shown.

The analysis approaches presented in this submission are summarised in Table 17. In addition, OC analysis results are reported for HiSCR endpoints, disease flare, worst skin pain response and DLQI MCID response. Only OC data are available for week 48 HiSCR endpoints among patients with a week 16 response (because the mNRI for HS-ABX models failed to converge), and for the EQ-5D-3L.

Table 17 Analyses presented in this submission

Endpoint	ICE definition used in MI/mNRI analyses	Individual trial/pooled trial data	Individual/pooled bimekizumab 320 mg Q2W arms at week 16	Location in submission
Primary endpoint (HiSCR50 at week 16)	All-ABX (prespecified analysis)	Individual	Pooled	Appendix D.5
	HS-ABX (*post hoc* analysis)	Individual	Individual and pooled	B.2.6.3
Key secondary endpoints (week 16)	HS-ABX	Individual	Individual (except pain outcomes)	B.2.6.4.1 (HiSCR75) B.2.6.8 (flare) B.2.6.9 (DLQI, pain outcomes)
Other week 16 endpoints	HS-ABX	Pooled	Individual (except DLQI MCID and HiSQOL)	B.2.6.4.2 (HiSCR25,-90,-100) B.2.6.6 (AN count; DT count) B.2.6.7 (IHS4) B.2.6.9 (DLQI MCID, pain outcomes, HiSQOL, EQ-5D-3L)
All week 48 endpoints	HS-ABX	Pooled (individual also provided for flare)	Individual (except HiSQOL)	B.2.6.5 (HiSCR responses) B.2.6.6 (AN count; DT count) B.2.6.7 (IHS4) B.2.6.8 (flare) B.2.6.9 (HSSQ 0, DLQI, HiSQOL, EQ-5D-3L)

ABX, antibiotics; DLQI, Dermatology Life Quality Index; HiSCR, hidradenitis suppurativa clinical response; HiSQOL, hidradenitis suppurativa quality of life; HS, hidradenitis suppurativa; ICE, intercurrent event; MCID, minimal clinically important difference; Q2W, every 2 weeks.

B.2.6.2 Statistical significance of primary and key secondary endpoints at week 16 according to prespecified analysis

The statistical significance of the BE HEARD trial primary and key secondary endpoints at week 16 using the prespecified mNRI for all-ABX analysis, in which the definition of an intercurrent event includes any systemic antibiotic use (see section B.2.4.2), is shown in Appendix D.5, Table 116. The results of the mNRI for all-ABX analyses – which were required for regulatory purposes and do not match expected clinical practice or the secukinumab phase 3 trials – are also shown in Appendix D.5, with the relevant tables for each outcome cross-referenced within this section.

In BE HEARD I, the primary endpoint of HiSCR50 at week 16 was statistically significant at the 0.025 level in the bimekizumab 320 mg Q2W group, compared with the placebo group, as were HiSCR75 and absolute change from baseline in DLQI total score and worst HS skin pain. No endpoints were statistically significant in the bimekizumab 320 mg Q4W group compared with the placebo group [1].

In BE HEARD II, HiSCR50 and HiSCR75 were statistically significant at the 0.025 level in both bimekizumab 320 mg Q2W and Q4W groups compared with the placebo group. According to the statistical testing procedure shown in section B.2.4.4, Figure 5, no other endpoints were statistically significant in either group [2].

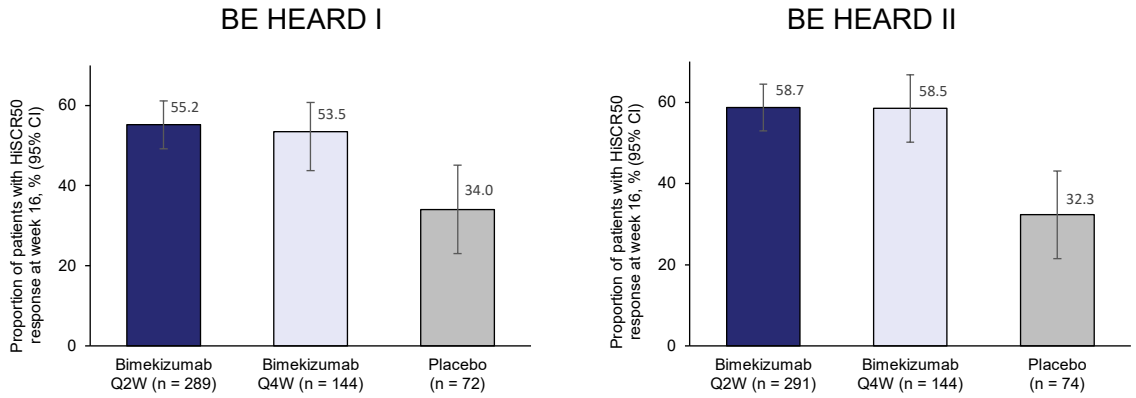
The results described in the remainder of section B.2.6 are reported according to the alternative *post hoc* analysis, in which the use of systemic antibiotics for reasons other than HS was not considered to be an intercurrent event (see section B.2.4.3), and no *p* values are presented.

B.2.6.3 HiSCR50 response at week 16

Patients treated with bimekizumab 320 mg Q2W were more likely to achieve HiSCR50 at week 16 than those receiving placebo

In the analysis using mNRI for HS-ABX, 55.2% of patients treated with bimekizumab 320 mg Q2W in BE HEARD I achieved HiSCR50 at week 16, compared with 34.0% in the placebo group (Figure 6) [119, 120]. In BE HEARD II, a week 16 HiSCR50 response was achieved by 58.7% of patients treated with bimekizumab 320 mg Q2W and 32.3% of those receiving placebo (Figure 6) [119, 120].

Figure 6 HiSCR50 response at week 16 (RS: mNRI for HS-ABX)



mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
ABX, antibiotics; CI, confidence interval; HiSCR, hidradenitis suppurativa clinical response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; Q2W, every 2 weeks; Q4W, every 4 weeks.
Source: BE HEARD I and II data tables [119, 120].

For consistency with other analyses, HiSCR50 responses by maintenance phase treatment group (mNRI for HS-ABX and OC analyses) are shown in Table 18 [115].

The results of the mNRI for all-ABX analysis, in which the primary endpoint was met in both bimekizumab Q2W groups, are shown in Appendix D.5, Table 117.

Table 18 HiSCR50 results at week 16 in BE HEARD trials (RS: mNRI for HS-ABX; OC)

Analysis	BE HEARD I				BE HEARD II			
	BKZ 320 mg Q2W/ Q2W (n = 143)	BKZ 320 mg Q2W/ Q4W (n = 146)	BKZ 320 mg Q4W/ Q4W (n = 144)	PBO (n = 72)	BKZ 320 mg Q2W/ Q2W (n = 145)	BKZ 320 mg Q2W/ Q4W (n = 146)	BKZ 320 mg Q4W/ Q4W (n = 144)	PBO (n = 74)
mNRI for HS-ABX analysis								
HiSCR50, % (95% CI)	59.8 (51.4, 68.2)	50.4 (42.1, 58.8)	53.5 (45.0, 62.0)	34.0 (23.0, 45.1)	56.1 (47.9, 64.4)	61.1 (52.9, 69.2)	58.5 (50.2, 66.8)	32.3 (21.5, 43.1)
OC analysis								
HiSCR50, n/N (%)	80/126 (63.5%)	71/131 (54.2%)	72/124 (58.1%)	24/65 (36.9%)	80/133 (60.2%)	84/132 (63.6%)	80/133 (60.2%)	24/70 (34.3%)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.
ABX, antibiotics; BKZ, bimekizumab; CI, confidence interval; HiSCR, hidradenitis suppurativa clinical response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set.
Source: Kimball 2023, AAD presentation [115]; BE HEARD I and II data tables [119, 120].

B.2.6.4 Treatment responses using other HiSCR thresholds

B.2.6.4.1 HiSCR75 response at week 16

Patients were more likely to achieve HiSCR75 with bimekizumab 320 mg Q2W than with placebo

Across bimekizumab 320 mg Q2W induction groups, 37.4–40.5% of patients achieved HiSCR75 at week 16, compared with 15.7% and 18.3% in the two placebo groups (mNRI for HS-ABX analysis [115]. Similar results were seen in the OC analysis (Table 19) [115].

Week 16 results for HiSCR75 assessed with mNRI for all-ABX are shown in Appendix D.5, Table 118.

B.2.6.4.2 HiSCR25, HiSCR90 and HiSCR100 responses at week 16

Patients were more likely to achieve HiSCR25, HiSCR90 and HiSCR100 with bimekizumab 320 mg Q2W than with placebo

[redacted]

In the mNRI for HS-ABX analysis, 22.0% of patients in the pooled bimekizumab 320 mg Q2W/Q4W groups had HiSCR90 responses at week 16, as did 21.0% in the pooled bimekizumab 320 mg Q2W/Q2W groups, compared with 8.5% in the pooled placebo group [129]. The corresponding proportions achieving HiSCR100 at week 16 were 15.6% and 16.6% in the two groups treated with bimekizumab 320 mg Q2W, compared with 5.6% in the placebo group (Table 20) [129].

Table 19 HiSCR75 results at week 16 in BE HEARD trials (RS: mNRI for HS-ABX; OC)

Analysis	BE HEARD I				BE HEARD II			
	BKZ 320 mg Q2W/ Q2W (n = 143)	BKZ 320 mg Q2W/ Q4W (n = 146)	BKZ 320 mg Q4W/ Q4W (n = 144)	PBO (n = 72)	BKZ 320 mg Q2W/ Q2W (n = 145)	BKZ 320 mg Q2W/ Q4W (n = 146)	BKZ 320 mg Q4W/ Q4W (n = 144)	PBO (n = 74)
mNRI for HS-ABX analysis								
HiSCR75, % (95% CI)	39.9 (31.6, 48.3)	37.4 (29.4, 45.5)	31.4 (23.5, 39.4)	18.3 (9.3, 27.3)	38.8 (30.7, 46.9)	40.5 (32.3, 48.7)	36.4 (28.3, 44.5)	15.7 (7.2, 24.1)
OC analysis								
HiSCR75, n/N (%)	54/126 (42.9%)	53/131 (40.5%)	42/124 (33.9%)	13/65 (20.0%)	56/133 (42.1%)	56/132 (42.4%)	51/133 (38.3%)	12/70 (17.1%)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.

OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.

BKZ, bimekizumab; CI, confidence interval; HiSCR, hidradenitis suppurativa clinical response; mNRI, modified non-responder imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set.

Source: Kimball 2023, AAD presentation [115]; BE HEARD I and II Integrated Summary of Efficacy tables [123].

Table 20 HiSCR25, HiSCR90 and HiSCR100 responses at week 16 (pooled BE HEARD RS: mNRI for HS-ABX; OC)

Response threshold	Bimekizumab 320 mg Q2W/Q2W (n = 288)	Bimekizumab 320 mg Q2W/Q4W (n = 292)	Bimekizumab 320 mg Q4W/Q4W (n = 288)	Placebo (n = 146)
mNRI for HS-ABX analysis				
HiSCR25, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR90, % (95% CI)	21.0 (16.1, 25.8)	22.0 (17.2, 26.9)	20.6 (15.7, 25.4)	8.5 (3.9, 13.1)
HiSCR100, % (95% CI)	15.6 (11.2, 19.9)	16.6 (12.2, 21.1)	15.8 (11.4, 20.2)	5.6 (1.8, 9.4)
OC analysis				
HiSCR25, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR90, n/N (%)	56/259 (21.6%)	60/263 (22.8%)	55/257 (21.4%)	13/135 (9.6%)
HiSCR100, n/N (%)	40/259 (15.4%)	45/263 (17.1%)	42/257 (16.3%)	8/135 (5.9%)

Mnri for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.
ABX, antibiotics; BKZ: bimekizumab; CI, confidence interval; HiSCR, hidradenitis suppurativa clinical response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; OC, observed case; RS, randomised set; Q2W, every 2 weeks; Q4W, every 4 weeks.
Source: Zouboulis 2023a, EADV presentation [129]; BE HEARD pooled data tables [121].

B.2.6.5 HiSCR responses up to week 48

B.2.6.5.1 HiSCR50, HiSCR75, HiSCR90 and HiSCR100 responses up to week 48

Bimekizumab 320 mg Q2W/Q4W is associated with rapid HiSCR50 responses and response levels maintained up to week 48

In the pooled BE HEARD patient population groups treated with bimekizumab 320 mg Q2W, 34.1% (Q2/Q2W) and 40.1% (Q2W/Q4W) of patients had HiSCR50 responses as early as week 4, with 55.9% (Q2W/Q4W) and 58.0% (Q2W/Q2W) achieving HiSCR50 at week 16 (mNRI for HS-ABX analysis; Figure 7) [129]. Response levels were maintained during maintenance treatment with bimekizumab 320 mg Q4W, with 62.6% of patients in the bimekizumab 320 mg Q2W/Q4W group having a HiSCR50 response at week 48 (mNRI for HS-ABX analysis).

In the OC analysis, 80.6% of patients treated with bimekizumab 320 mg Q2W/Q4W had a HiSCR50 response at week 48 (Figure 8) [129]. Higher response rates at week 48 are seen in the OC analysis due to the accumulation in the mNRI for HS-ABX analysis of imputed non-response following intercurrent events (see section B.2.11.2 for discussion).

HiSCR75, HiSCR90 and HiSCR100 response levels achieved with bimekizumab 320 mg Q2W at week 16 were maintained to week 48 with bimekizumab Q4W maintenance therapy

In the mNRI for HS-ABX analysis, the proportions of patients in the pooled bimekizumab 320 mg Q2W/Q4W group who had HiSCR75, HiSCR90 and HiSCR100 responses generally increased from week 16 to week 48 (Figure 7) [129]. At week 48, 33.0% of patients treated

with bimekizumab 320 mg Q2W/Q4W group had a HiSCR90 response, and 23.3% achieved HiSCR100 [129].

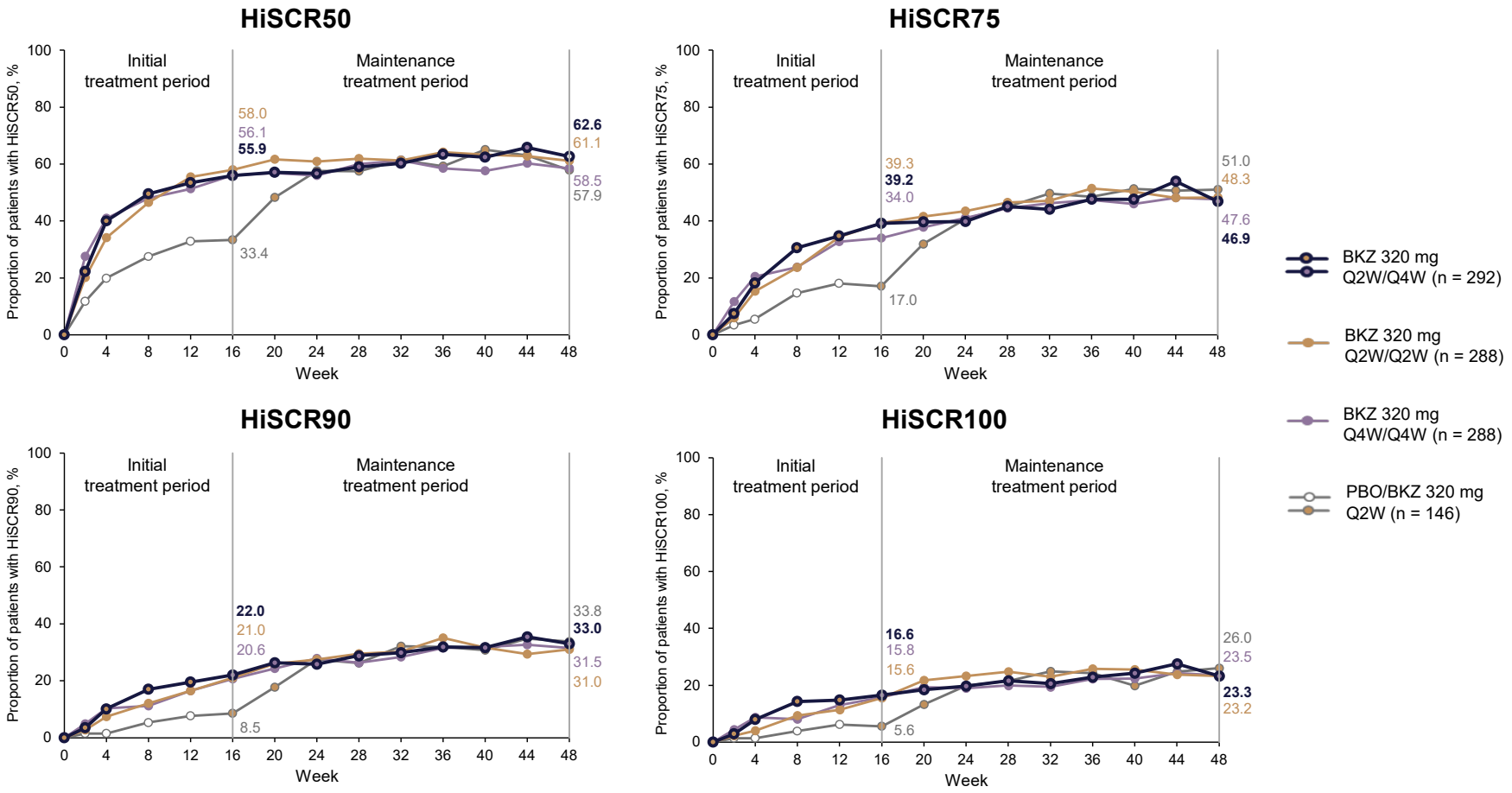
In the OC analysis 60.2% of patients receiving bimekizumab 320 mg Q2W/Q4W achieved HiSCR75 at week 48 and 28.9% had a HiSCR100 response (Figure 8) [129].

B.2.6.5.2 Retention of HiSCR50, HiSCR75 and HiSCR90 responses during maintenance treatment period

Most patients retained their week 16 HiSCR50, HiSCR75 and HiSCR90 responses during maintenance treatment with bimekizumab 320 mg Q4W

Among patients with a week 16 HiSCR50 response following treatment with bimekizumab 320 mg Q2W, 88.5% retained this response at week 48 after bimekizumab 320 mg Q4W maintenance treatment (OC analysis; Figure 9) [130]. A similar proportion of patients retained week 16 HiSCR75 responses (88.3%) [130]. In addition, 69.2% of patients treated with bimekizumab 320 mg Q2W/Q4W who achieved HiSCR90 at week 16 retained this response at week 48 (Figure 9) [130].

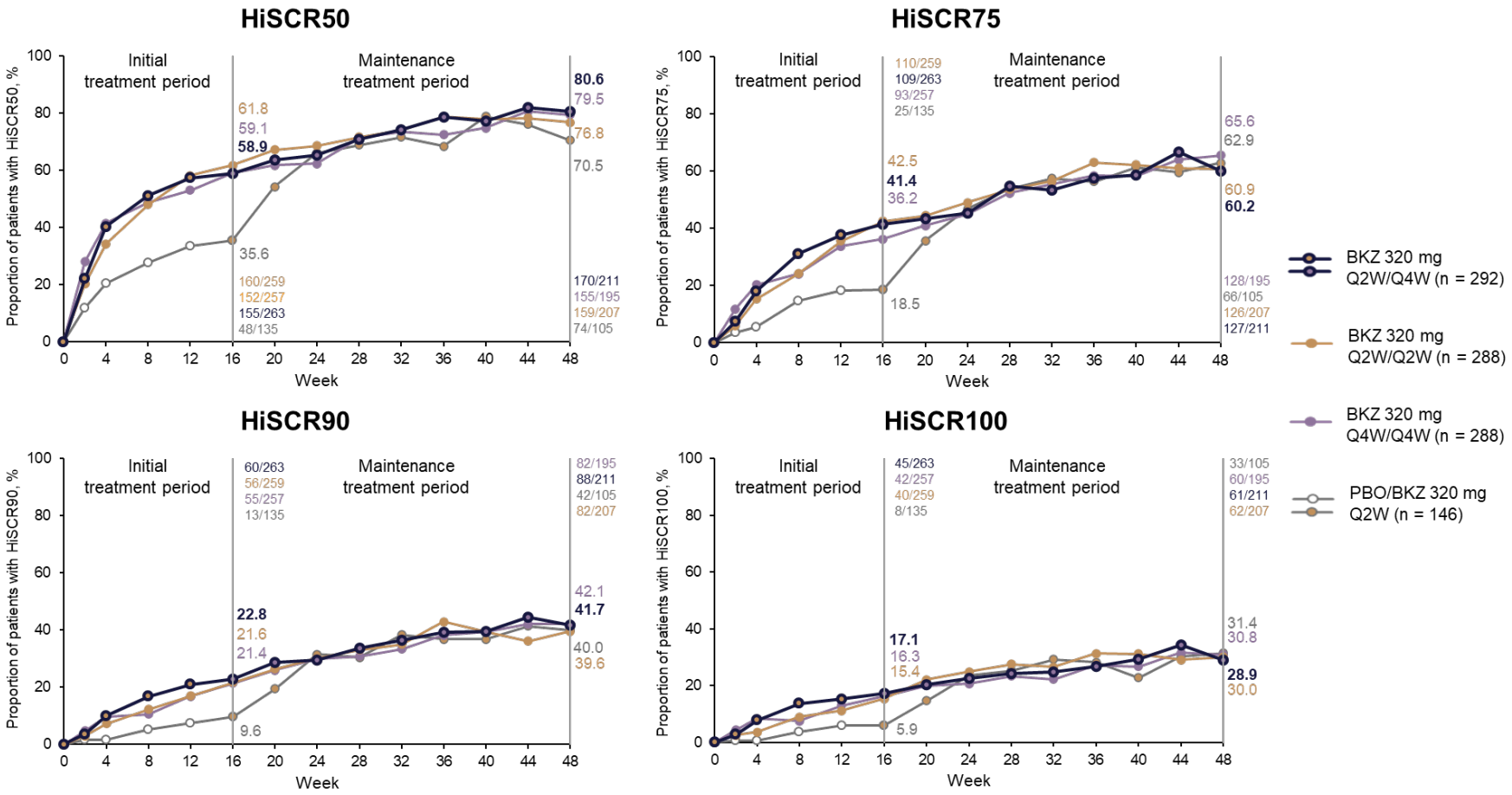
Figure 7 HiSCR50, HiSCR75, HiSCR90 and HiSCR100 responses up to week 48 in pooled BE HEARD population (RS: mNRI for HS-ABX)



mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.

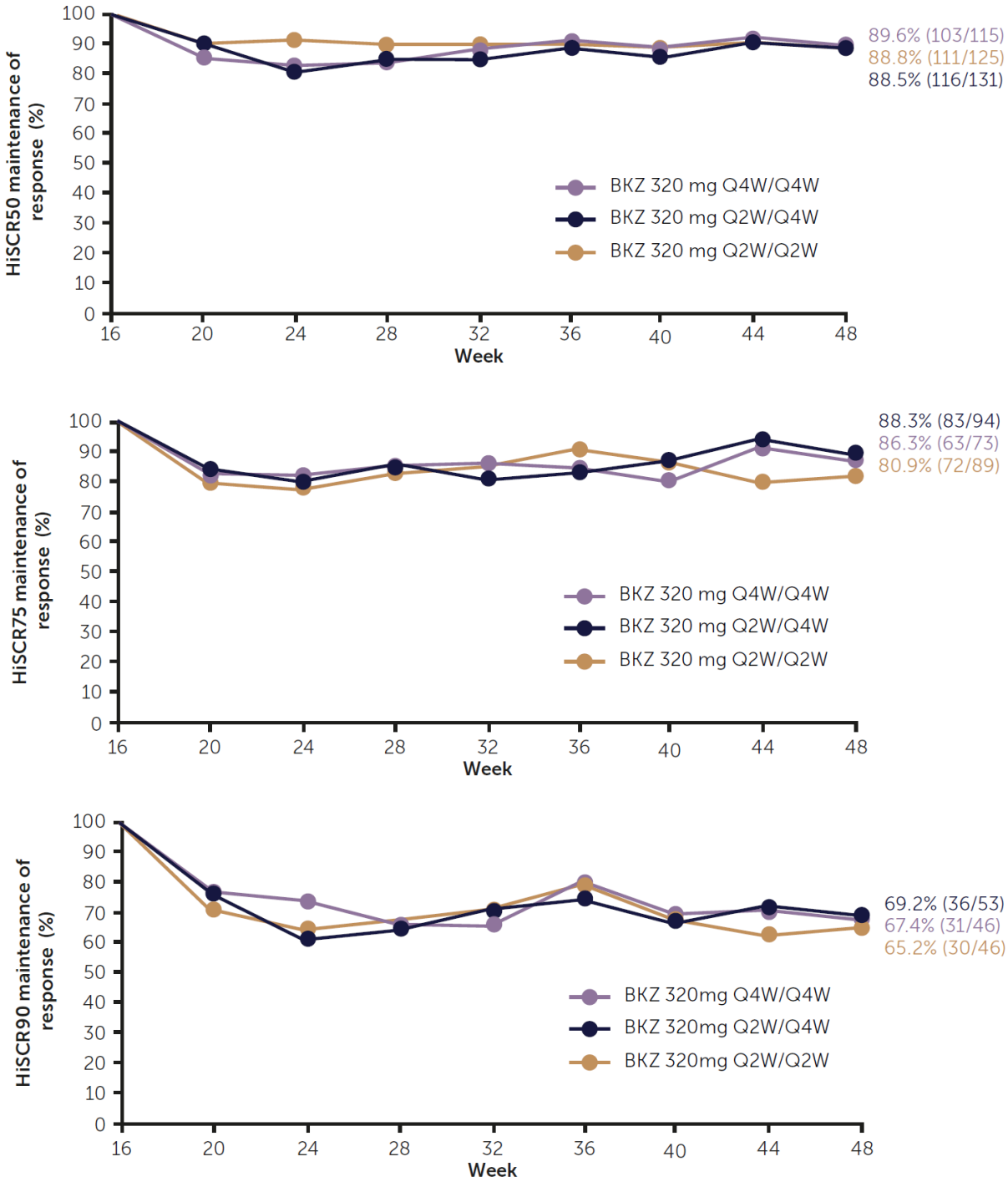
ABX, antibiotics; HiSCR, hidradenitis suppurativa clinical response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set. Source: Zouboulis 2023a, EADV presentation [129].

Figure 8 HiSCR50, HiSCR75, HiSCR90 and HiSCR100 responses up to week 48 in pooled BE HEARD population (RS: OC)



OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.
HiSCR, hidradenitis suppurativa clinical response; HS, hidradenitis suppurativa; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set.
Source: Zouboulis 2023a, EADV presentation [129].

Figure 9 HiSCR50, HiSCR75 and HiSCR90 responses among week 16 responders in pooled BE HEARD population (MS: OC)



OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.

No mNRI for HS-ABX analysis was possible for these data due to convergence issues as of the result of the small numbers of patients in each group.

BKZ, bimekizumab; HiSCR, hidradenitis suppurativa clinical response; MS, maintenance set; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks.

Source: Ingram 2023, EADV presentation [130].

B.2.6.6 Improvement in HS lesions

B.2.6.6.1 Improvement in abscess and inflammatory nodule count

Patients treated with bimekizumab 320 mg Q2W/Q4W had larger mean percentage reductions in AN count at week 16 than those receiving placebo

At week 16, patients in the pooled bimekizumab 320 mg Q2W/Q4W group had a mean 53.8% reduction in AN count (see section B.2.3.1.6, Table 9), compared with a 28.2% reduction in the placebo group (Table 21) [123].

For patients treated with bimekizumab 320 mg Q2W/Q4W, the reduction in AN count increased during maintenance treatment, to 72.0% at week 48 (Figure 10) [123].

Table 21 Mean percentage change from baseline in AN lesion count from baseline to week 16 in pooled BE HEARD population (RS: MI for HS-ABX)

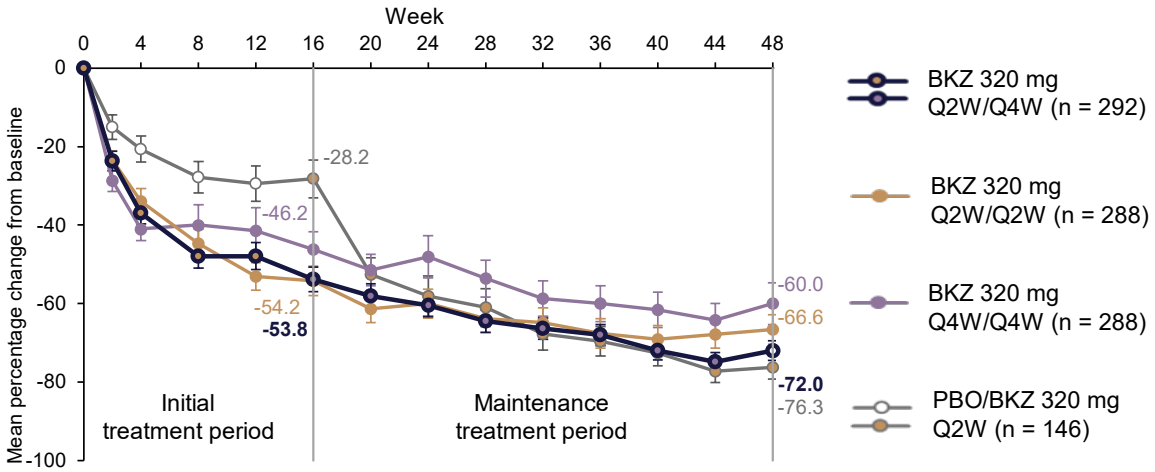
Percentage change from baseline to week 16, mean (SE)	Bimekizumab 320 mg Q2W/Q2W (n = 288)	Bimekizumab 320 mg Q2W/Q4W (n = 292)	Bimekizumab 320 mg Q4W/Q4W (n = 288)	Placebo/ bimekizumab 320 mg Q2W (n = 146)
AN count	−54.2% (3.8%)	−53.8% (3.1%)	−46.2% (4.5%)	−28.2% (4.8%)

MI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as having experienced an intercurrent event. Intermittent 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 multiple imputation method for missing data.

ABX, antibiotics; AN, abscess and inflammatory nodule; HS, hidradenitis suppurativa; MCMC, Markov chain Monte Carlo imputation; MI, multiple imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set; SE, standard error.

Source: BE HEARD I and II Integrated Summary of Efficacy data tables [123].

Figure 10 Mean percentage change in AN lesion count from baseline to week 48 in pooled BE HEARD population (RS: MI for HS-ABX)



Error bars indicate SE.

MI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as having experienced an intercurrent event. Intermittent 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 multiple imputation method for missing data.

ABX, antibiotics; AN, abscess and inflammatory nodule; HS, hidradenitis suppurativa; MCMC, Markov chain Monte Carlo imputation; MI, multiple imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set; SE, standard error.

Source: BE HEARD I and II Integrated Summary of Efficacy data tables [123].

B.2.6.6.2 Improvement in draining tunnel count

Patients treated with bimekizumab 320 mg Q2W/Q4W had larger mean reductions in DT count at week 16 than those receiving placebo

Reductions in DT count (see section B.2.3.1.6, Table 9) during the BE HEARD trials are shown in Figure 11 and Table 22. Patients treated with bimekizumab 320 mg Q2W/Q4W had larger mean reductions in DT count from baseline to week 16 than those treated with placebo (−1.6 vs −0.4); the mean reduction at week 48 in the bimekizumab 320 mg Q2W/Q4W group was −2.0 (MI for HS-ABX) [138].

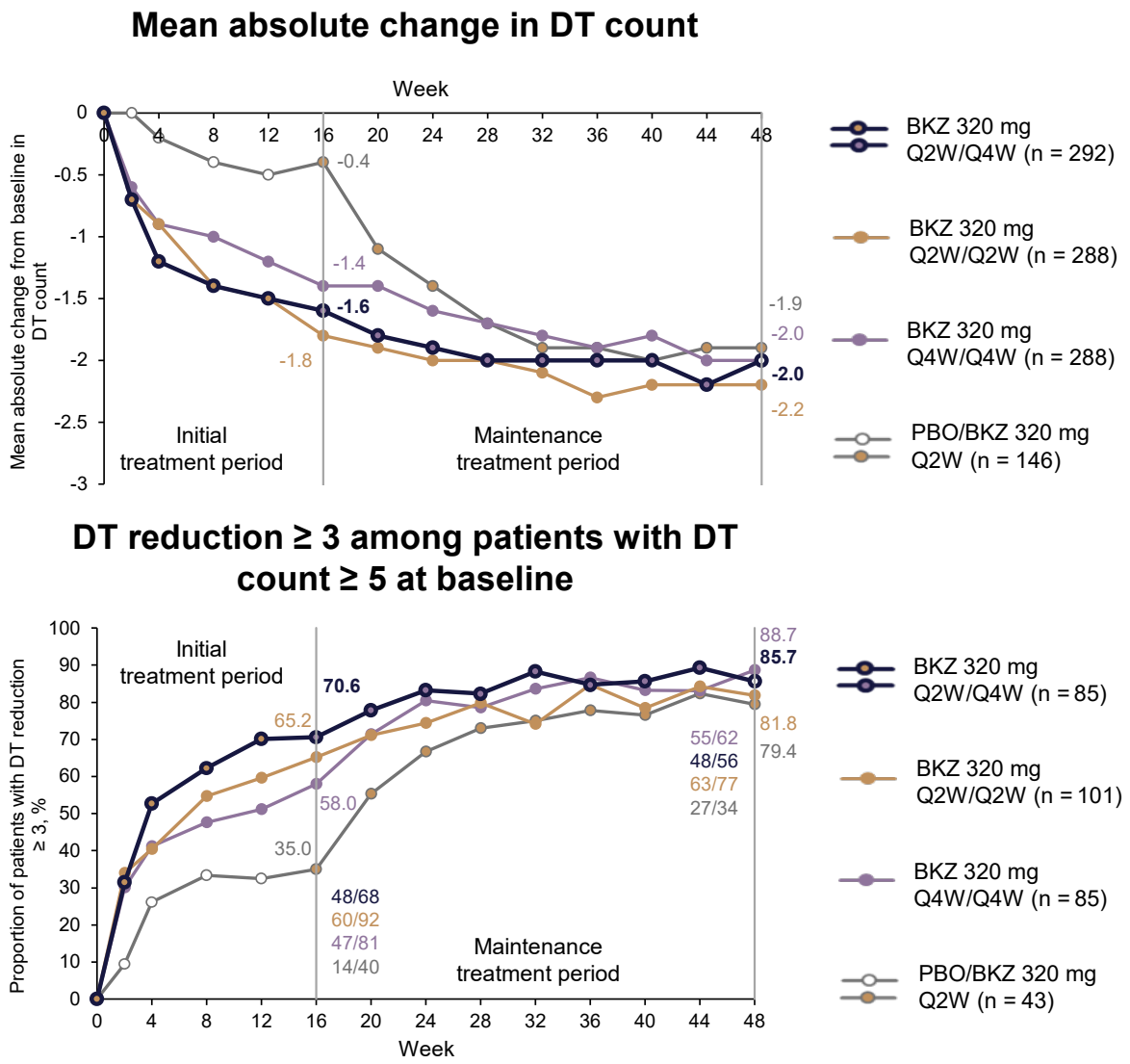
At week 48, 44.3% of patients in the bimekizumab 320 mg Q2W/Q4W group achieved zero DTs

At week 48, 44.3% of patients in the bimekizumab 320 mg Q2W/Q4W group had achieved zero DTs (mNRI for HS-ABX analysis; Table 22) [138]. Among those with > 5 DTs at baseline, 21.7% of patients in the bimekizumab 320 mg Q2W/Q4W group achieved zero DTs at week 48 (mNRI for HS-ABX analysis; Table 22) [138].

Among patients with ≥ 5 DTs at baseline, a larger proportion achieved a reduction of at least 3 DTs at week 16 in the bimekizumab 320 mg Q2W/Q4W group than in the placebo group (mNRI for HS-ABX analysis, 61.0% [95% CI, 54.6–67.5%] vs 30.5% [16.7–44.4%]; Table 22) [138]. There was a further increase in the proportion of patients in the bimekizumab 320 mg

Q2W/Q4W group with a reduction of at least 3 DTs at week 48 (mNRI for HS-ABX analysis, 66.2% [95% CI, 58.5–74.0%]) [138].

Figure 11 Reductions in DT count to week 48 in pooled BE HEARD population (RS: MI for HS-ABX; OC)



DT reduction ≥ 3 was analysed among patients with ≥ 5 DTs at baseline.
MI for HS-ABX (mean absolute change): patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as missing at all subsequent visits.
OC (DT reduction ≥ 3): n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.
DT, draining tunnel; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set.
Source: Zouboulis 2024 AAD presentation [138].

Table 22 Reduction in DT count from baseline to week 16 and week 48 in pooled BE HEARD population (RS: mNRI for HS-ABX; OC)

	Bimekizumab 320 mg Q2W/Q2W	Bimekizumab 320 mg Q2W/Q4W	Bimekizumab 320 mg Q4W/Q4W	Placebo/ bimekizumab 320 mg Q2W
LS mean change from baseline				
Baseline N	580		288	146
LS mean change (95% CI) at week 16 [MI for HS-ABX]	−1.453 (−1.760, −1.146)		−1.399 (−1.779, −1.019)	−0.370 (−0.849, 0.109)
Overall, patients achieving 0 DTs				
Baseline N	288	292	288	146
Proportion of patients at week 48, % (95% CI) [mNRI for HS-ABX]	42.6% (36.4–48.8%)	44.3% (38.3–50.4%)	44.0% (38.0–50.1%)	43.9% (35.3–52.5%)
Proportion of patients at week 48, n/N (%) [OC]	113/207 (54.6%)	121/211 (57.3%)	113/195 (57.9%)	59/105 (56.2%)
Patients with > 5 DTs at baseline achieving 0 DTs				
Baseline N	75	65	57	32
Proportion of patients at week 48, % (95% CI) [mNRI for HS-ABX]	20.5% (11.0–30.0%)	21.7% (11.3–32.1%)	13.1% (3.7–22.5%)	17.7% (3.8–31.5%)
Proportion of patients at week 48, n/N (%) [OC]	16/56 (28.6%)	16/46 (34.8%)	7/41 (17.1%)	7/24 (29.2%)
Patients with ≥ 5 DTs at baseline achieving ≥ 3 DT reduction				
Baseline N	101	76	85	43
Proportion of patients at week 16, % (95% CI) [mNRI for HS-ABX]	61.6% (56.1–67.2%)	61.0% (54.6–67.5%)	57.2% (49.7–64.7%)	30.5% (16.7–44.4%)
Proportion of patients at week 48, % (95% CI) [mNRI for HS-ABX]	66.1% (59.4–72.8%)	66.2% (58.5–74.0%)	67.5% (60.4–74.6%)	59.5% (44.6–74.4%)
Proportion of patients at week 48, n/N (%) [OC]	63/77 (81.8%)	48/56 (85.7%)	55/62 (88.7%)	27/34 (79.4%)

MI for HS-ABX (mean absolute change): patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as missing at all subsequent visits.
mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.
ABX, antibiotics; CI, confidence interval; DT, draining tunnel; HS, hidradenitis suppurativa; LS, least squares; MI, multiple imputation; mNRI, modified non-responder imputation; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set.
Source: Zouboulis 2024 AAD presentation [138].

B.2.6.7 IHS4 severity

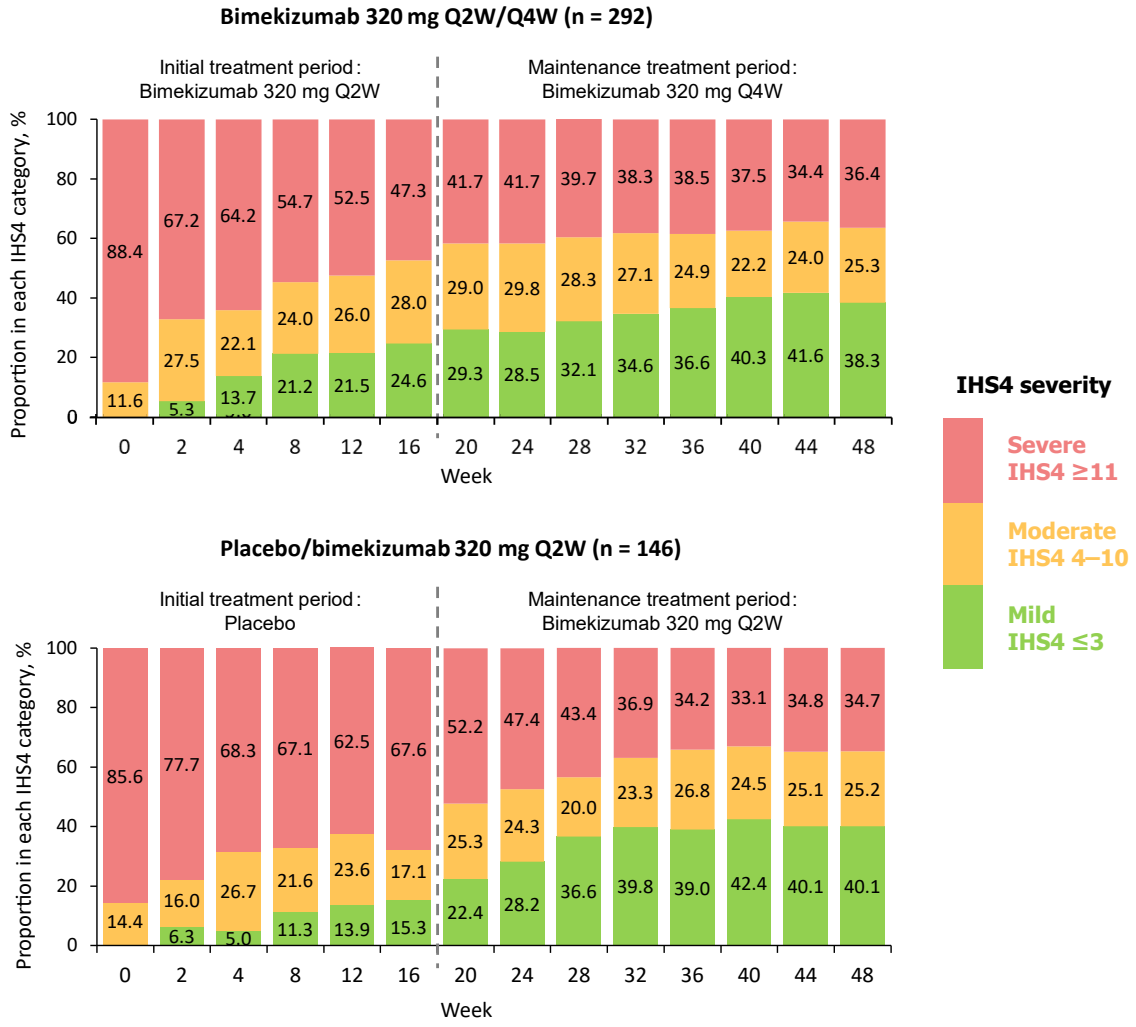
Treatment with bimekizumab 320 mg Q2W/Q4W was associated with a sustained reduction in disease severity

The IHS4 is described in section B.1.3.1.2. The main advantage of the IHS4 compared to HiSCR is that DT burden can be more comprehensively measured, as well as abscess and inflammatory nodules [16, 17]. The established IHS4 disease severity bands are: mild, ≤ 3 points; moderate, 4–10 points; severe, ≥ 11 points [16, 17].

At baseline, all patients in the BE HEARD trials had moderate or severe disease according to IHS4 (Figure 12) [131]. In the pooled bimekizumab 320 mg Q2W/Q4W treatment group, 88.4% of patients had severe disease at baseline. At week 16, after the initial treatment period, 47.3% had severe disease and 24.6% had mild disease [131]. This trend continued during maintenance treatment with bimekizumab 320 mg Q4W: at week 48, only 36.4% of patients had severe disease and 38.3% had mild disease (Figure 12) [131].

In the placebo group, 67.6% of patients had severe disease at week 16 [131]. After treatment with bimekizumab 320 mg Q2W during the maintenance treatment period, the proportion of patients with severe disease dropped to 34.7%, with 40.1% only having mild disease at week 48 (Figure 12) [131].

Figure 12 IHS4 severity to week 48 in pooled BE HEARD population (RS: MI for HS-ABX)



MI for HS-ABX: Participants who experienced an intercurrent event were treated as missing following the intercurrent event. Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as missing at all subsequent visits. BKZ, bimekizumab; HS, hidradenitis suppurativa; IHS4, International HS Severity Scoring System; MI, multiple imputation; PBO, placebo; RS, randomised set; Q2W, every 2 weeks; Q4W, every 4 weeks. Source: Zouboulis 2023b EADV presentation [131].

Patients were more likely to achieve IHS4-55 at week 16 with bimekizumab 320 mg Q2W than with placebo

The IHS4-55 is a dichotomous version of the IHS4 defined as a 55% reduction in total score (see section B.1.3.1.2). In the pooled BE HEARD trial population, 53.5% of patients treated with bimekizumab 320 mg Q2W/Q4W achieved IHS4-55 at week 16, compared with 26.2% of those receiving placebo (mNRI for HS-ABX analysis; Table 23) [121].

Table 23 IHS5-55 responses at week 16 in pooled BE HEARD population (RS: mNRI for HS-ABX; OC)

Proportion with IHS4-55 response	Bimekizumab 320 mg Q2W/Q2W (n = 288)	Bimekizumab 320 mg Q2W/Q4W (n = 292)	Bimekizumab 320 mg Q4W/Q4W (n = 288)	Placebo/ bimekizumab 320 mg Q2W (n = 146)
mNRI, HS-ABX, % (95% CI)	53.1% (47.1–59.0%)	53.5% (47.7–59.4%)	52.7% (46.7–58.7%)	26.2% (19.0–33.5%)
OC, n/N (%)	146/259 (56.4%)	150/263 (57.0%)	144/257 (56.0%)	38/135 (28.1%)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.
ABX, antibiotics; CI, confidence interval; HS, hidradenitis suppurativa; IHS4, International Hidradenitis Suppurativa Severity Score System; IHS4-55, 55% reduction in IHS4 total score; mNRI, modified non-responder imputation; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set.
Source: BE HEARD I and II pooled data analysis tables [121].

B.2.6.8 Flare

Patients treated with bimekizumab 320 mg Q2W/Q4W were less likely to have flares during the initial treatment period than those receiving placebo

Flare was defined as at least a 25% increase in AN count with an absolute increase of ≥ 2 AN relative to baseline at a given study visit. During the 16-week initial treatment period, 22.6% and 19.0% of patients in the BE HEARD I and BE HEARD II bimekizumab 320 mg Q2W/Q4W groups, respectively, were experiencing flares at one or more study visits (mNRI for HS-ABX analysis; Table 24) [119, 120]. The corresponding proportions in the two placebo groups were 39.5% and 25.2%, respectively [119, 120]. Similar results were seen in the OC analysis (Table 24) [119, 120].

During maintenance treatment, the proportion of patients in the pooled bimekizumab 320 mg Q2W/Q4W experiencing a flare at any specific study visit (OC analysis) was low, with 1.4% of patients having a flare at week 48 (Figure 13) [121].

Table 24 Proportion of patients with flare in BE HEARD trials (RS: mNRI for HS-ABX; OC)

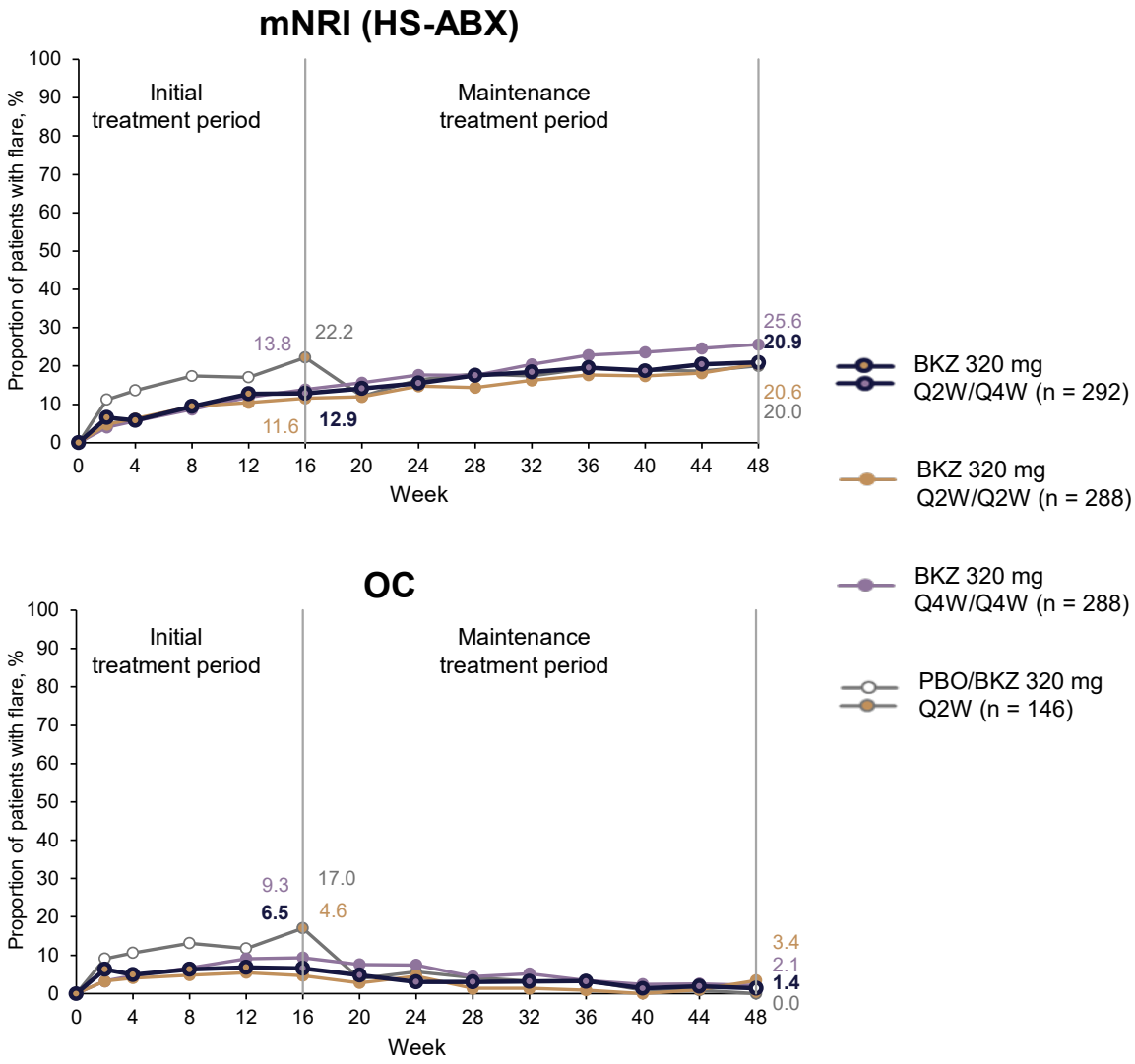
Proportion with flare	BE HEARD I				BE HEARD II			
	BKZ 320 mg Q2W/ Q2W (n = 143)	BKZ 320 mg Q2W/ Q4W (n = 146)	BKZ 320 mg Q4W/ Q4W (n = 144)	PBO/ BKZ 320 mg Q2W (n = 72)	BKZ 320 mg Q2W/ Q2W (n = 145)	BKZ 320 mg Q2W/ Q4W (n = 146)	BKZ 320 mg Q4W/ Q4W (n = 144)	PBO/ BKZ 320 mg Q2W (n = 74)
Flare at any time during initial treatment period								
mNRI, HS-ABX, % (95% CI)	15.2% (9.0, 21.4%)	22.6% (15.6, 29.6%)	24.7% (17.4, 32.0%)	39.5% (28.1, 50.9%)	21.4% (14.6, 28.2%)	19.0% (12.5, 25.6%)	16.5% (10.3, 22.7%)	25.2% (15.1, 35.2%)
OC, n/N (%)	14/140 (10.0%)	20/144 (13.9%)	25/140 (17.9%)	25/71 (35.2%)	21/143 (14.7%)	21/145 (14.5%)	18/142 (12.7%)	15/73 (20.5%)
Flare at any time during maintenance treatment period								
mNRI, HS-ABX, % (95% CI)	26.9% (19.2, 34.6%)	27.8% (20.1, 35.6%)	36.1% (27.8, 44.3%)	34.7% (23.2, 46.2%)	25.0% (17.6, 32.3%)	25.7% (18.4, 32.9%)	27.7% (20.2, 35.2%)	15.7% (7.2, 24.2%)
OC, n/N (%)	13/128 (10.2%)	17/126 (13.5%)	17/123 (13.8%)	5/65 (7.7%)	11/130 (8.5%)	10/128 (7.8%)	19/133 (14.3%)	7/69 (10.1%)

MI for HS-ABX: Participants who experienced an intercurrent event were treated as experiencing a flare following the intercurrent event. Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as missing at all subsequent visits.

OC: n/N denominator represents number of patients with a non-missing lesion count, and percentages are calculated accordingly.

ABX, antibiotics; BKZ, bimekizumab; CI, confidence interval; HS, hidradenitis suppurativa; MCMC, Markov chain Monte Carlo imputation; MI, multiple imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks. Source: BE HEARD I and II data tables [119, 120].

Figure 13 Proportion of patients with flare to week 48 in pooled BE HEARD population (RS: mNRI for HS-ABX; OC)



mNRI for HS-ABX: Participants who experienced an intercurrent event were treated as experiencing a flare following the intercurrent event. Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as non-responders at all subsequent visits.

OC: n/N denominator represents number of patients with a non-missing lesion count, and percentages are calculated accordingly.

BKZ, bimekizumab; MCMC, Markov chain Monte Carlo imputation; MI, multiple imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks.

Source: BE HEARD I and II pooled analysis data tables [121].

The proportion of patients with an HS flare during the initial treatment period was a secondary endpoint in BE HEARD II – results of the prespecified analysis imputing any systemic antibiotic use as a disease flare are shown in Appendix D.5, Table 119 [2].

B.2.6.9 Patient-reported outcomes and health-related quality of life

B.2.6.9.1 Pain

Patients treated with bimekizumab 320 mg Q2W had larger mean improvements in worst daily skin pain than those receiving placebo

Change from baseline to week 16 in the "worst skin pain" item (11-point NRS) in the HSSDD is shown in Table 25. In the overall study population, the mean change from baseline to week 16 in the bimekizumab 320 mg Q2W group was −1.98 in BE HEARD I and −1.87 in BE HEARD II, compared with −0.92 and −0.45 in the corresponding placebo groups [121].

Table 25 Change from baseline to week 16 in worst skin pain NRS in BE HEARD trials (RS: MI for HS-ABX)

Worst skin pain NRS, mean (SE)	BE HEARD I			BE HEARD II		
	BKZ 320 mg Q2W (n = 289)	BKZ 320 mg Q4W (n = 144)	PBO (n = 72)	BKZ 320 mg Q2W (n = 291)	BKZ 320 mg Q4W (n = 144)	PBO (n = 74)
Baseline	5.45 (0.16)	5.91 (0.22)	5.89 (0.32)	5.33 (0.15)	5.27 (0.21)	4.94 (0.30)
Change from baseline to week 16	−1.98 (0.18)	−1.44 (0.25)	−0.92 (0.32)	−1.87 (0.16)	−1.52 (0.24)	−0.45 (0.30)

MI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as having experienced an intercurrent event. Intermittent 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 multiple imputation method for missing data.

ABX, antibiotics; BKZ, bimekizumab; CI, confidence interval; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set.

Source: BE HEARD I and II data tables [119-121].

Change in worst skin pain NRS score from baseline to week 16, analysed using imputation following any systemic antibiotic use, was a secondary endpoint in the BE HEARD trials [1, 2]. Results for this analysis are shown in Appendix D.5, Table 121 [1, 2].

Patients treated with bimekizumab 320 mg Q2W were more likely to have HSSDD worst skin pain responses than those receiving placebo

Skin pain response was defined as at least a 3-point decrease from baseline in HSSDD weekly worst skin pain score among study participants with a score of ≥ 3 at baseline, which is considered to be a clinically meaningful change [1, 2]. At week 16, 36.7% of patients in both BE HEARD bimekizumab 320 mg Q2W groups had a skin pain response, compared with 16.1% and 11.1% in the two placebo groups (mNRI for HS-ABX analysis; Table 26) [123].

Worst skin pain NRS response, analysed using imputation following any systemic antibiotic use, was a secondary endpoint in the BE HEARD trials [1, 2]. Results for this analysis are shown in Appendix D.5, Table 122 [1, 2].

Table 26 HSSDD worst skin pain NRS response at week 16 in BE HEARD trials (RS: mNRI for HS-ABX; OC)

Proportion with worst skin pain NRS response	BE HEARD I			BE HEARD II		
	BKZ 320 mg Q2W (n = 289)	BKZ 320 mg Q4W (n = 144)	PBO (n = 72)	BKZ 320 mg Q2W (n = 291)	BKZ 320 mg Q4W (n = 144)	PBO (n = 74)
mNRI for HS-ABX, % (95% CI)	36.7% (29.4, 44.1%)	25.3% (16.0, 34.7%)	16.1% (4.5, 27.8%)	36.7% (29.8, 43.6%)	32.9% (23.5, 42.4%)	11.1% (1.8, 20.4%)
OC, n/N (%)	55/138 (39.9%)	21/66 (31.8%)	4/26 (15.4%)	62/163 (38.0%)	28/78 (35.9%)	4/42 (9.5%)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing lesion count, and percentages are calculated accordingly.
Skin pain response was defined as at least a 3-point decrease from baseline in HSSDD weekly worst skin pain score among study participants with a score of ≥ 3 at baseline.
ABX, antibiotics; BKZ, bimekizumab; CI, confidence interval; HS, hidradenitis suppurativa; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary; mNRI, modified non-responder imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set.
Source: BE HEARD I and II Integrated Summary of Efficacy tables [123].

Patients were more likely to achieve NRS30 skin pain responses at week 16 with bimekizumab 320 mg Q2W than with placebo

An alternative definition of skin pain response, NRS30 (a ≥ 30% reduction and reduction of ≥ 2 units from baseline in HSSDD of Skin Pain by “worst skin pain” on a continuous numerical rating scale, assessed in patients with a baseline HSSDD score of ≥ 3; see section B.2.3.1.6) was also explored. In the pooled BE HEARD trial population, 49.9% of patients treated with bimekizumab 320 mg Q2W achieved an NRS30 response at week 16, compared with 26.9% of those receiving placebo (mNRI for HS-ABX analysis; Table 27) [121].

Table 27 NRS30 responses at week 16 in pooled BE HEARD population (RS: mNRI for HS-ABX; OC)

Proportion with NRS30 response	Bimekizumab 320 mg Q2W (n = 399)	Bimekizumab 320 mg Q4W (n = 211)	Placebo (n = 95)
mNRI for HS-ABX, % (95% CI)	49.9% (44.7–55.0%)	43.6% (36.1–51.1%)	26.9% (17.1–36.7%)
OC, n/N (%)	161/301 (53.5%)	72/144 (50.0%)	20/68 (29.4%)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.
NRS30, a ≥ 30% reduction and reduction of ≥ 2 units from baseline in HSSDD weekly worst skin pain NRS score, assessed in patients with a baseline HSSDD score of ≥ 3.
ABX, antibiotics; CI, confidence interval; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; NRS, numerical rating scale; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set. Source: BE HEARD I and II pooled data analysis tables [121].

Patients were more likely to achieve HSSQ 0 skin pain responses at week 16 with bimekizumab 320 mg Q2W than with placebo

A further definition of skin pain response, a Hidradenitis Suppurativa Symptom Questionnaire (HSSQ) score of 0 – indicating no skin pain – among patients with baseline scores ≥ 1, also showed higher response rates for bimekizumab Q2W than for placebo at week 16 (Table 28). The proportion of patients with HSSQ 0 increased from week 16 to week 48 in all groups [139].

Table 28 HSSQ 0 skin pain responses among patients with baseline HSSQ ≥ 1 in pooled BE HEARD population (RS: mNRI for HS-ABX; OC)

Proportion with HSSQ 0 response	Bimekizumab 320 mg Q2W/Q2W	Bimekizumab 320 mg Q2W/Q4W	Bimekizumab 320 mg Q4W/Q4W	Placebo/ bimekizumab 320 mg Q2W
mNRI for HS-ABX analysis				
Week 16, *% (95% CI)*	10.8% (8.6–12.9%)	7.1% (5.3–8.9%)	7.3% (5.0–9.5%)	2.3% (0.0–4.8%)
Week 48, *% (95% CI)*	15.5% (12.3–18.7%)	11.3% (8.5–14.2%)	14.2% (11.1–17.3%)	14.5% (8.2–20.7%)
OC analysis				
Week 16, n/N (%)	29/249 (11.6%)	19/256 (7.4%)	18/250 (7.2%)	3/129 (2.3%)
Week 48, n/N (%)	39/197 (19.8%)	26/205 (12.7%)	36/187 (19.3%)	17/97 (17.5%)

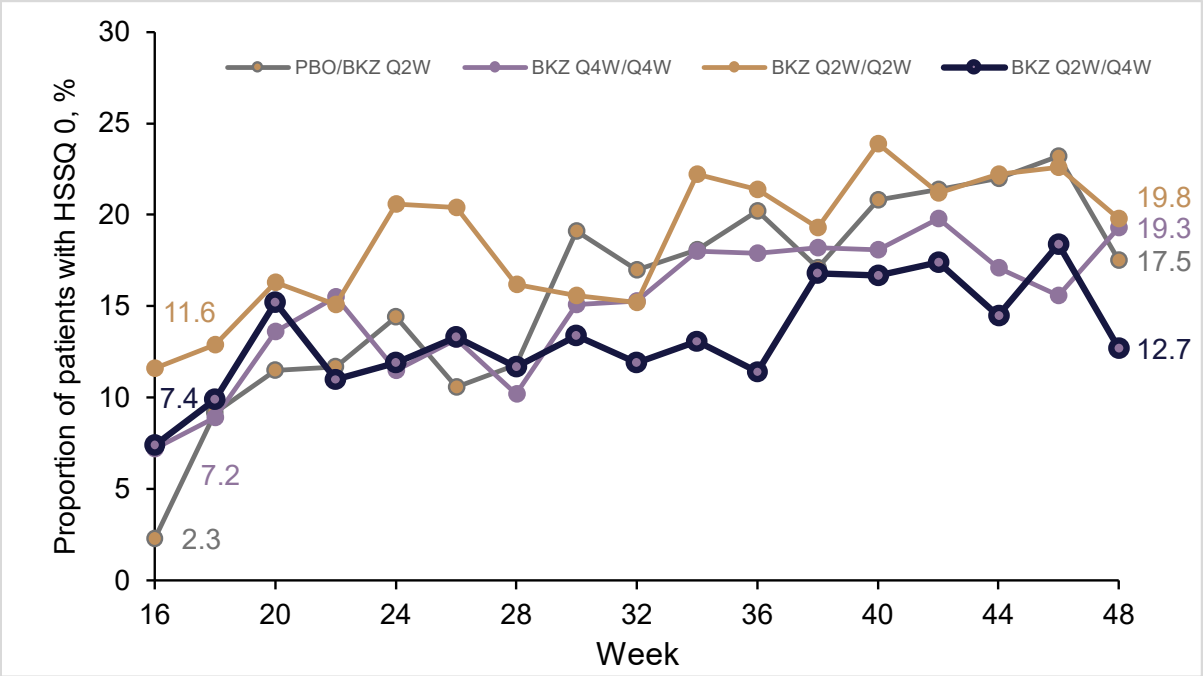
mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.

OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.

ABX, antibiotics; CI, confidence interval; HS, hidradenitis suppurativa; HSSQ, Hidradenitis Suppurativa Symptom Questionnaire; mNRI, modified non-responder imputation; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set.

Source: Orenstein 2024, AAD presentation [139].

Figure 14 HSSQ 0 skin pain responses among patients with baseline HSSQ ≥ 1 in pooled BE HEARD population (MS: OC)



OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.
ABX, antibiotics; HSSQ, Hidradenitis Suppurativa Symptom Questionnaire; MS, maintenance set; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks.
Source: Orenstein 2024, AAD presentation [139].

B.2.6.9.2 HSSDD symptoms other than pain

Changes from baseline to week 16 in HSSDD smell or odour, worst itch, and drainage or oozing scores, analysed using imputation following any systemic antibiotic use (MI for all-ABX), are shown in Appendix D.5, Table 123 [122]. In the pooled BE HEARD population, larger improvements were seen in both bimekizumab groups than in the placebo group [122].

B.2.6.9.3 DLQI

Patients treated with bimekizumab 320 mg Q2W had larger mean DLQI improvements than those receiving placebo

At baseline, DLQI was numerically higher in the groups randomised to placebo than those randomised to bimekizumab 320 mg Q2W/Q4W. Change from baseline to week 16 in DLQI is shown in Table 29 (MI for HS-ABX). The mean change from baseline to week 16 in the BE HEARD I and BE HEARD II bimekizumab 320 mg Q2W/Q4W groups was −4.3 and −4.2, respectively, compared with −2.9 and −3.2 in the corresponding placebo groups [123].

Similar improvements from baseline in mean DLQI score were seen during the maintenance treatment period (Figure 15) [123].

Table 29 Mean change from baseline to week 16 in DLQI in BE HEARD trials (RS: MI for HS-ABX)

DLQI	BE HEARD I				BE HEARD II			
	BKZ 320 mg Q2W/ Q2W (n = 143)	BKZ 320 mg Q2W/ Q4W (n = 146)	BKZ 320 mg Q4W/ Q4W (n = 144)	PBO/ BKZ 320 mg Q2W (n = 72)	BKZ 320 mg Q2W/ Q2W (n = 145)	BKZ 320 mg Q2W/ Q4W (n = 146)	BKZ 320 mg Q4W/ Q4W (n = 144)	PBO/ BKZ 320 mg Q2W (n = 74)
Baseline score, mean (SE)	11.8 (0.6)	11.0 (0.6)	12.8 (0.6)	12.6 (0.9)	10.7 (0.5)	10.5 (0.6)	10.6 (0.6)	12.2 (0.7)
Change from baseline, mean (SE)	−5.6 (0.5)	−4.3 (0.5)	−5.4 (0.6)	−2.9 (0.8)	−5.0 (0.5)	−4.2 (0.5)	−4.5 (0.5)	−3.2 (0.6)

MI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as having experienced an intercurrent event. Intermittent 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 multiple imputation method for missing data.
ABX, antibiotics; BKZ, bimekizumab; CI, confidence interval; DLQI, Dermatology Life Quality Index; HS, hidradenitis suppurativa; MCMC, Markov chain Monte Carlo imputation; MI, multiple imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set; SE, standard error.
Source: BE HEARD I and II Integrated Summary of Efficacy data tables [123].

Change in DLQI total score from baseline to week 16, analysed using imputation following any systemic antibiotic use, was a secondary endpoint in the BE HEARD trials [1, 2]. Results for this analysis are shown in Appendix D.5, Table 120 [1, 2].

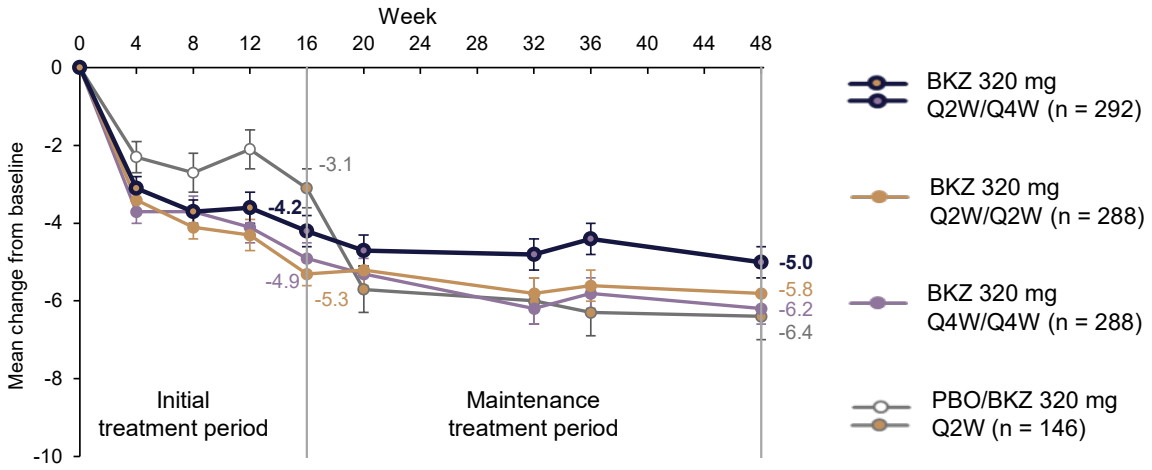
Patients treated with bimekizumab 320 mg Q2W were more likely than those receiving placebo to achieve a minimal clinically important difference in DLQI at week 16

DLQI minimal clinically important difference (MCID) responses were defined as a ≥ 4-point improvement among patients with baseline scores ≥ 4 [146].

As shown in Table 30, 56.4% of patients in the pooled BE HEARD population who had baseline DLQI ≥ 4 and were treated with bimekizumab 320 mg Q2W had a DLQI improvement of ≥ 4-points at week 16, 10.5% higher than the response rate seen in the placebo group (mNRI for HS-ABX analysis) [136]. A similar difference between bimekizumab 320 mg Q2W and placebo groups was seen in the OC analysis (Table 30) [136].

DLQI MCID response rates were consistent during the maintenance treatment period, with 51.4% of patients treated with bimekizumab 320 mg Q2W/Q4W having a response at week 48 (mNRI for HS-ABX analysis; Figure 16) [121].

Figure 15 Mean change from baseline to week 48 in DLQI in pooled BE HEARD population (RS: MI for HS-ABX)



Error bars indicate SE.

MI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as having experienced an intercurrent event. Intermittent 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 multiple imputation method for missing data.

ABX, antibiotics; BKZ, bimekizumab; HS, hidradenitis suppurativa; MCMC, Markov chain Monte Carlo imputation; MI, multiple imputation; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set; SE, standard error.

Source: BE HEARD I and II Integrated Summary of Efficacy data tables [123].

Table 30 DLQI MCID responses at week 16 in pooled BE HEARD population (RS: mNRI for HS-ABX; OC)

Analysis	BKZ 320 mg Q2W (n = 496)	BKZ 320 mg Q4W (n = 245)	PBO (n = 125)
mNRI for HS-ABX analysis			
DLQI MCID response, % (95% CI)	56.5 (52.0–60.9)	59.9 (53.6–66.2)	45.9 (37.0–54.9)
OC analysis			
DLQI MCID response, n/N (%)	267/447 (59.7%)	139/219 (63.5%)	56/114 (49.1%)

DLQI MCID was defined as a ≥ 4-point reduction from baseline in DLQI total score in patients with baseline DLQI ≥ 4.

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.

OC: n/N denominator represents number of patients with a non-missing DLQI total score, and percentages are calculated accordingly.

BKZ, bimekizumab; MCID, minimal clinically important difference; mNRI, modified non-responder imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set.

Source: BE HEARD I and II pooled analysis data tables [121]; Mayo 2023, SHSA presentation [136].

Figure 16 DLQI MCID responses to week 48 in pooled BE HEARD population (RS: mNRI for HS-ABX; OC) (confidential)

DLQI MCID was defined as a ≥ 4-point reduction from baseline in DLQI total score in patients with baseline DLQI ≥ 4.
mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing DLQI total score, and percentages are calculated accordingly.
ABX, antibiotics; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set.
Source: BE HEARD I and II pooled analysis data tables [121].

B.2.6.9.4 HiSQOL

Patients treated with bimekizumab had greater improvements in HiSQOL total score between baseline and week 16 than those receiving placebo

Changes from baseline in HiSQOL total score and domain scores are shown in Table 31 [132]. At week 16, greater improvements in HiSQOL total score were reported for patients treated with bimekizumab 320 mg, compared with those receiving placebo. Following the switch to bimekizumab 320 mg Q2W in the placebo group, at week 48 improvements were comparable between groups. HiSQOL improvements were observed across all individual domains at week 16, with bimekizumab treatment leading to a numerically greater improvement, compared with the placebo group [132].

Table 31 HiSQOL total score and domain scores at baseline, and mean change from baseline to week 16 and week 48 in pooled BE HEARD population (MI for HS-ABX)

HiSQOL domain (possible range)	Bimekizumab 320 mg (all groups; n = 868)			Placebo/bimekizumab 320 mg (n = 146)		
	Baseline	Week 16	Week 48	Baseline	Week 16	Week 48
Total Score (0–68)	25.0 (13.3)	−11.0 (0.4)	−13.4 (0.5)	26.5 (14.1)	−5.8 (0.9)	−14.5 (1.2)
Symptoms domain (0–16)	7.9 (0.1)	−2.6 (0.1)	−3.4 (0.1)	8.2 (0.3)	−1.4 (0.3)	−3.8 (0.4)
Psychosocial domain (0–20)	5.2 (0.1)	−2.3 (0.1)	−2.7 (0.1)	5.9 (0.4)	−1.4 (0.3)	−3.3 (0.4)
Activities-adaptation domain (0–32)	11.9 (0.2)	−6.0 (0.2)	−7.2 (0.3)	12.4 (0.6)	−3.1 (0.5)	−7.3 (0.6)

Data are mean (SD) at baseline for total score, mean (SE) at baseline for domain scores, and mean (SE) changes from baseline to week 16 or week 48.

MI for HS-ABX: patients who discontinued study treatment due to lack of efficacy/adverse events, or who received systemic antibiotics identified as rescue medication for HS by the principal investigator, were set to missing and subsequently imputed using the MI method for missing data.

ABX, antibiotics; HS, hidradenitis suppurativa; HiSQOL, Hidradenitis Suppurativa Quality of Life; MI, multiple imputation; SD, standard deviation; SE, standard error.

Source: BE HEARD I and II pooled HiSQOL data tables [122]; Kirby *et al.* 2023, SHSA presentation [132].

B.2.6.9.5 EQ-5D-3L

Patients treated with bimekizumab 320 mg Q2W/Q4W had larger mean increases in EQ-5D-3L scores at week 16 than those receiving placebo

Baseline EQ-5D-3L scores ranged from [redacted] across randomised groups (Table 32) [121]. The mean increase from baseline to week 16 was greater ([redacted]) among patients treated with bimekizumab 320 mg Q2W/Q4W, compared with [redacted] in the placebo group (OC analysis; Table 32) [121]. The improvement in the bimekizumab 320 mg Q2W/Q4W group was slightly increased at week 48 (Figure 15) [121].

Health state utilities in the economic model described in section B.3.4.1 are derived from BE HEARD EQ-5D-3L data.

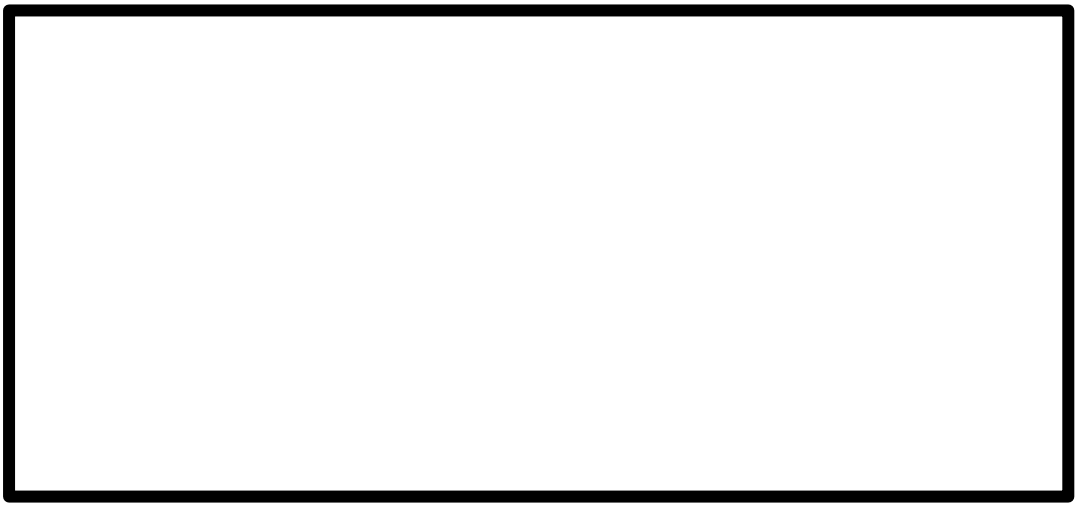
Table 32 EQ-5D-3L change from baseline to week 16 and week 48 in pooled BE HEARD population (RS: OC)

EQ-5D-3L	Bimekizumab 320 mg Q2W/Q2W (n = 288)	Bimekizumab 320 mg Q2W/Q4W (n = 292)	Bimekizumab 320 mg Q4W/Q4W (n = 288)	Placebo/ bimekizumab 320 mg Q2W (n = 146)
Baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]

OC, observed case; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set; SE, standard error.

Source: BE HEARD I and II pooled analysis data tables [121].

Figure 17 EQ-5D-3L change from baseline to week 48 in pooled BE HEARD population (RS: OC) (confidential)



Error bars indicate SE.

OC, observed case; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; Q2W, every 2 weeks; Q4W, every 4 weeks; RS, randomised set; SE, standard error.

Source: BE HEARD I and II pooled analysis data tables [121].

B.2.6.10 Summary of additional trial data

B.2.6.10.1 Open-label extension study – 2-year data

As described in section B.1.3.3, it is common for patients treated with the currently available biological therapies for HS, adalimumab and secukinumab, to have an initial clinical response but lose this response by the end of 1 year of treatment [44-48].

For bimekizumab, long-term maintenance of treatment responses is being investigated in the BE HEARD EXT extension study, which patients in the BE HEARD I and BE HEARD II trials were eligible to enter at the end of the parent studies.

As described in section B.2.3.1.1, patients were assigned to receive bimekizumab 320 mg Q2W or Q4W, according to their HiSCR90 response status, calculated using the average lesion count from weeks 36, 40 and 44 in BE HEARD I and BE HEARD II [118]. Data for all eight BE HEARD EXT treatment groups are shown in Appendix D.6, Table 124.

The treatment groups most relevant to the decision problem are those including patients treated with bimekizumab 320 mg initial treatment (Q2W up to week 16) followed by bimekizumab 320 mg Q4W maintenance treatment (up to week 48) in the BE HEARD trials who then go on to receive either bimekizumab 320 mg Q4W or Q2W in BE HEARD EXT. Data for these groups and for the overall BE HEARD EXT population are summarised in Table 33. The bimekizumab 320 mg Q2W/Q4W/Q4W group corresponds to patients treated with bimekizumab Q2W/Q4W in the BE HEARD trials who had a HiSCR90 response on average over weeks 36–44; the bimekizumab 320 mg Q2W/Q4W/Q2W group consists of patients who did not have such a response.

Safety results for the BE HEARD EXT trial are summarised in section B.2.10.3.

Table 33 Summary of BE HEARD EXT results at week 96 (OLE set: OC; MI for HS-ABX)

Endpoint	Week	BKZ 320 mg Q2W/ Q4W/Q4W (n = 75)	BKZ 320 mg Q2W/Q4W/ Q2W (n = 115)	BKZ 320 mg total (n = 556)
OC analysis, n/N (%)				
HiSCR50	Week 48	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]
HiSCR75	Week 48	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]
HiSCR90	Week 48	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]
HiSCR100	Week 48	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]
IHS4-55	Week 48	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]
MI for HS-ABX analysis, % (95% CI)				
IHS4 mild	Week 48	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]
IHS4 moderate	Week 48	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]
IHS4 severe	Week 48	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]

OC (all outcomes except IHS4 severity): n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.
MI for HS-ABX (IHS4 severity): patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as having experienced an intercurrent event. Intermittent 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 multiple imputation method for missing data.
ABX, antibiotics; BKZ, bimekizumab; CI, confidence interval; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; IHS4, International Hidradenitis Suppurativa Severity Score System; MI, multiple imputation; mNRI, modified non-responder imputation; NC, not calculable; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks.

HiSCR50, HiSCR75, HiSCR90 and HiSCR100 responses

As a result of the design of BE HEARD EXT, patients in the bimekizumab 320 mg Q2W/Q4W/Q4W group had high rates of HiSCR50, HiSCR75, HiSCR90 and HiSCR100 responses at week 48. [redacted]

IHS4 endpoints

[redacted]

B.2.6.10.2 Phase 2 study

Bimekizumab for the treatment of moderate to severe HS was investigated in a phase 2, proof-of-concept, double-blind, placebo-controlled randomised clinical trial in which

participants were randomised to bimekizumab (640 mg at week 0 then 320 mg Q2W), placebo or adalimumab (160 mg at week 0, 80 mg at week 2 then 40 mg weekly (QW) at weeks 4–10) for 12 weeks. Bimekizumab dosing in the phase 2 trial is different from the target licence, and these data are provided as supporting information only.

Adalimumab was included as a reference arm in this trial [116]. The adalimumab reference arm was not designed to test equivalence, superiority or non-inferiority of bimekizumab compared to adalimumab. There were no pre-specified analyses directly comparing the bimekizumab and adalimumab treatment arms, nor were statistical comparisons made between placebo and adalimumab; however, the results shown in Table 34do not appear to signal any inferiority of bimekizumab compared with adalimumab.

The phase 2 trial was powered to compare bimekizumab with placebo using a Bayesian statistical analysis method using an informative prior from PIONEER II [46] for placebo and a vague prior for bimekizumab [116]. Patients who had previously used anti–IL-17 or TNFi therapies were excluded from the phase 2 trial; the study population is therefore not directly comparable with the BE HEARD trials [116].

Full results from the phase 2 trial have been published [116]; key findings are summarised in Table 34 and Figure 18. In brief, patients treated with bimekizumab were more likely to achieve HiSCR50 at week 12 than those receiving placebo [116]. Bimekizumab was associated with numerically higher rates of HiSCR75 and HiSCR90 responses than placebo, as well as a with a greater likelihood of skin pain responses and DLQI scores of 0 or 1 (a score that indicates the disease has no effect at all on a patient's life [148]) [116]. Improvements in IHS4 score were larger with than with placebo [116].

Table 34 Week 12 results in phase 2 trial (NRI, OC)

Endpoint	Bimekizumab (n = 46)	Placebo (n = 21)	Adalimumab (n = 21)
Primary endpoint – HiSCR50			
Response rate, NRI	25/44 (57%)	5/20 (25%)	–
Response rate, observed	25/40 (63%)	5/18 (28%)	12/18 (67%)
Results of modelled posterior probability for HiSCR50			
Mean, % (SD)	57.3% (7.4%)	26.1% (6.8%)	–
Median, % (95% CI)	57.4% (42.4–71.4%)	25.7% (13.8–40.5%)	–
Mean posterior difference from placebo, % (SD) [95% CI]	31.2% (10.1%) [11.0–50.4%]	–	–
Probability difference vs placebo > 0%	99.8%	–	–
HiSCR75			
Response rate, OC	20/40 (50%)	2/18 (11%)	7/18 (39%)
HiSCR90			
Response rate, OC	14/40 (35%)	0/18 (0%)	3/18 (17%)
IHS4 score			
Baseline, mean (SD)	40.5 (29.8)	49.8 (34.7)	42.0 (26.1)
Week 12	16.0 (18.0)	40.2 (32.6)	16.5 (NR)
Patient's global assessment of skin pain response [a]			
≥ 30% reduction, OC	27/42 (64%)	7/19 (37%)	9/18 (50%)
≥ 1-unit reduction, OC	30/42 (71%)	9/19 (47%)	11/18 (61%)
≥ 30% and ≥ 1-unit reduction, OC	27/42 (64%)	7/19 (37%)	9/18 (50%)
DLQI 0/1 (remission)			
Response rate, OC	14/39 (36%)	0/20 (0%)	3/21 (14%)

Unless otherwise specified, data are n/N (%).

For HiSCR50, Bayesian analysis was performed in which the posterior probability distribution for the difference in between bimekizumab-treated and placebo-treated participants confirmed that the superiority criteria for bimekizumab were met. NRI: participants who received rescue therapy (analgesics, abscess incision/drainage or intralesional triamcinolone injections) were considered non-responders. Concomitant antibiotic therapy was permitted during this phase 2 study.

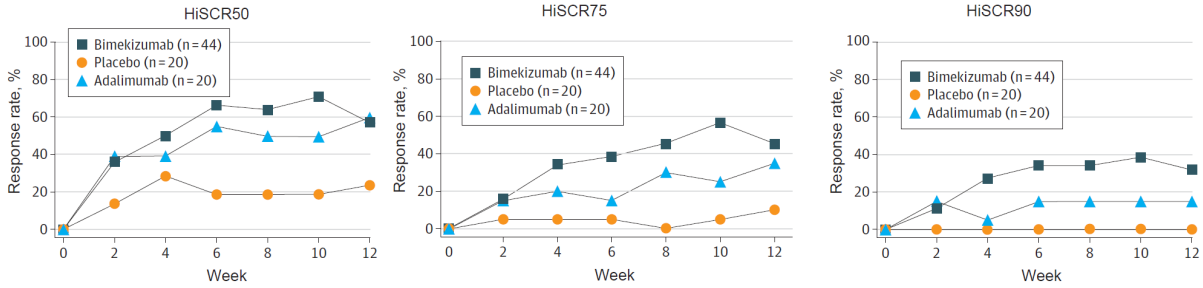
[a] Patient's global assessment of skin pain was judged as pain at its worst in the last 24 hours, using an 11-point NRS.

CI, confidence interval; DLQI, Dermatology life Quality Index; HiSCR, hidradenitis suppurativa clinical response; IHS4, International Hidradenitis Suppurativa Severity Score System; NR, not reported; NRI, non-responder imputation; NRS, numerical rating scale; OC, observed case; SD, standard deviation.

Source: Glatt *et al.* 2021 [116].

Safety results for the phase 2 trial are summarised in section B.2.10.4 and in Appendix F, Table 131.

Figure 18 HiSCR50, HiSCR75 and HiSCR90 results to week 12 in phase 2 trial (NRI)



NRI: participants who received rescue therapy were considered non-responders.

HiSCR, hidradenitis suppurativa clinical response; NRI, non-responder imputation.

Source: Glatt *et al.* 2021 [116].

B.2.6.10.3 Real-world cohort

Data have recently been reported for a French cohort of patients with HS who had undergone multiple previous treatments, including multiple antibiotics and both anti-TNFi therapy (adalimumab and/or infliximab) and secukinumab [140]. Patients were treated with bimekizumab 320 mg Q4W for four months [140].

At 12 weeks, 64% (45/72) of patients had HiSCR50 responses, with 42% achieving HiSCR75 and 12% HiSCR90. The corresponding proportions at week 24 were: HiSCR50, 72%; HiSCR75, 48%; HiSCR90, 15% [140].

B.2.7 Subgroup analysis

B.2.7.1 Subgroup analyses conducted

The subgroup analyses specified in the BE HEARD trial protocols and included in this submission are HiSCR50 response at week 16 and week 48 according to: previous biologic experience (yes / no); systemic antibiotic use at randomisation (yes/no); weight (≤ 100 kg / > 100 kg); Hurley stage at baseline (II / III); sex (female / male) and race (black/other races) [1, 2, 123, 133-136].

B.2.7.2 Subgroup analysis results

The efficacy of bimekizumab 320 mg Q2W/Q4W was consistent among biologic-naïve and biologic-experienced patients

Subgroup results according to prior biologic use are shown in Table 35. Across prior biologic subgroups, higher levels of HiSCR50 response were seen at week 16 among patients treated with bimekizumab, compared with the placebo group (bimekizumab 320 mg Q2W/Q4W HiSCR50 responses at week 16: biologic-naïve, 57.4%; biologic-experienced, 49.4%; placebo responses at week 16: biologic-naïve, 34.5%; biologic-experienced, 27.6%; mNRI for HS-ABX analysis). Bimekizumab 320 mg Q2W/Q4W also demonstrated consistent efficacy in the maintenance of HiSCR50 responses to week 48, regardless of prior biologic use (bimekizumab 320 mg Q2W/Q4W HiSCR50 responses at week 48: biologic-naïve, 66.2%; biologic-experienced, 46.8%%; mNRI for HS-ABX analysis) [133]. A limitation of this analysis is that there were a small number of patients in the biologic-experienced groups.

Table 35 HiSCR50 response rate at week 16 and week 48 by prior biologic experience (RS: mNRI for HS-ABX; OC)

HiSCR50 responses	Placebo/BKZ 320 mg Q2W (n = 146)	BKZ 320 mg Q2W/Q4W (n = 292)	BKZ 320 mg Q2W/Q2W (n = 288)	BKZ 320 mg Q4W/Q4W (n = 288)
Biologic-naïve, n	117	236	229	241
Week 16 response rate, mNRI, %	34.5%	57.4%	58.4%	57.5%
Week 16 response rate, OC, n/N (%)	40/107 (37.4%)	128/212 (60.4%)	126/202 (62.4%)	129/214 (60.3%)
Week 48 response rate, mNRI, %	58.1%	66.2%	61.5%	60.8%
Week 48 response rate, OC, n/N (%)	60/82 (73.2%)	141/173 (81.5%)	124/158 (78.5%)	130/164 (79.3%)
Biologic-experienced, n	29	56	59	47
Week 16 response rate, mNRI, %	27.6%	49.4%	56.2%	49.0%
Week 16 response rate, OC, n/N (%)	8/28 (28.6%)	27/51 (52.9%)	34/57 (59.6%)	23/43 (53.5%)
Week 48 response rate, mNRI, %	50.4%	46.8%	59.9%	47.2%
Week 48 response rate, OC, n/N (%)	14/23 (60.9%)	29/38 (76.3%)	35/49 (71.4%)	25/31 (80.6%)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.

OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.

All prior biologic treatments received by patients were for HS; two patients initially included in the 'prior biologic use' subgroup were switched to the 'biologic-naive' subgroup, as they had not received true biologic therapy.

BKZ, bimekizumab; HiSCR, hidradenitis suppurativa clinical response; OC, observed case; mNRI, modified non-responder imputation; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; TNFi, tumour necrosis factor inhibitor.

Source: Sayed *et al.* 2023, EADV presentation [133].

Week 16 HiSCR50 response rates were similar across systemic antibiotic use subgroups

As shown in Table 36, higher levels of clinical response were seen among patients treated with bimekizumab 320 mg Q2W/Q4W than those receiving placebo, whether or not they were using systemic antibiotics at randomisation (bimekizumab 320 mg Q2W/Q4W HiSCR50 responses at week 16: no antibiotic use, 57.4%; antibiotic use, 39.9%; placebo responses at week 16: no antibiotic use, 35.1%; antibiotic use, 9.1%; mNRI for HS-ABX analysis) [123]. The proportion of patients with HiSCR50 responses at week 48 was also similar between subgroups (bimekizumab 320 mg Q2W/Q4W: no antibiotic use, 63.3%; antibiotic use, 56.1%; mNRI for HS-ABX analysis) [123]. It should be noted that few patients were using systemic antibiotics at randomisation, meaning that these findings should be interpreted with caution.

Table 36 HiSCR50 response rate at week 16 and week 48 by systemic antibiotic use at randomisation (RS: mNRI for HS-ABX; OC)

HiSCR50 responses	Placebo/BKZ 320 mg Q2W (n = 146)	BKZ 320 mg Q2W/Q4W (n = 292)	BKZ 320 mg Q2W/Q2W (n = 288)	BKZ 320 mg Q4W/Q4W (n = 288)
Systemic antibiotic use: no, n	135	264	256	270
Week 16 response rate, mNRI, %	35.1%	57.4%	57.3%	56.7%
Week 16 response rate, OC, n/N (%)	47/125 (37.6%)	145/238 (60.9%)	142/233 (60.9%)	145/241 (60.2%)
Week 48 response rate, mNRI, %	57.5%	63.3%	60.4%	58.0%
Week 48 response rate, OC, n/N (%)	68/96 (70.8%)	155/190 (81.6%)	144/189 (76.2%)	145/179 (81.0%)
Systemic antibiotic use: yes, n	11	28	29	18
Week 16 response rate, mNRI, %	9.1%	39.9%	63.9%	45.8%
Week 16 response rate, OC, n/N (%)	1/10 (10.0%)	10/25 (40.0%)	18/26 (69.2%)	7/16 (43.8%)
Week 48 response rate, mNRI, %	45.8%	56.1%	62.2%	56.9%
Week 48 response rate, OC, n/N (%)	6/9 (66.7%)	15/21 (71.4%)	15/18 (83.3%)	10/16 (62.5%)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.
BKZ, bimekizumab; HiSCR, hidradenitis suppurativa clinical response; OC, observed case; mNRI, modified non-responder imputation; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; TNFi, tumour necrosis factor inhibitor.
Source: BE HEARD I and II pooled analysis data tables [121].

Bimekizumab 320 mg Q2W/Q4W demonstrated consistent efficacy across multiple additional subgroups

HiSCR50 responses are presented by weight in Appendix E, Table 125. A similar proportion of patients achieved HiSCR50 responses at week 16 and week 48 in both weight categories

(≤ 100 kg / > 100 kg). At week 16, greater levels of clinical response were seen for patients treated with bimekizumab than for those receiving placebo, regardless of weight [134].

Subgroup results according to Hurley stage at baseline are shown in Appendix E, Table 126. Bimekizumab was more efficacious than placebo at week 16, as assessed by HiSCR50 response rate, in both Hurley stage subgroups. At week 48, improvements in HiSCR50 were maintained in both subgroups [135].

An analysis of HiSCR50 responses by sex is described in Appendix E, Table 127. HiSCR50 response rates were similar for male and female patients at both week 16 and week 48 [135].

Subgroup results according to race (black/African-American vs all other patients) are shown in Appendix E, Table 128. The results showed that bimekizumab was efficacious in both subgroups, although the small number of black/African-American patients means that the findings should be interpreted with caution [136].

B.2.8 Meta-analysis

An NMA was conducted to estimate the relative efficacy of bimekizumab, secukinumab and placebo at week 16, reflecting the comparators in the decision problem (see section B.2.9.1). In addition, an unanchored matching-adjusted indirect comparison (MAIC) of bimekizumab versus secukinumab at weeks 48–52 was conducted (see section B.2.9.3).

B.2.9 Indirect and mixed treatment comparisons

Full details of the methodology for the NMA and the SLR that was used to identify studies for inclusion in the evidence network are reported in Appendix D.1. As described in Appendix D.1, adalimumab was also included as a comparator in the NMA. For those outcomes for which data were available for adalimumab, the NMA results for adalimumab are not presented here as a comparison with adalimumab is not considered within scope, as explained further in section B.1.1. More comprehensive NMA results (including adalimumab) are presented in Appendix D.1.5.6.

Relevant outcome data reported at week 12 and week 16 were synthesised in an NMA. Week 12–16 efficacy outcomes assessed in an NMA and reported in this submission are HiSCR50, HiSCR75, HiSCR90, HiSCR100 (all mNRI for HS-ABX), IHS4-55 (mNRI for HS-ABX), change from baseline in IHS4 total score (MI for HS-ABX), percentage change in AN count (MI for HS-ABX), absolute change in DT count (MI for HS-ABX) and NRS30 skin pain response (mNRI for HS-ABX). Analysis imputation methods in the BE HEARD trials were aligned with those used in the secukinumab trials to minimise heterogeneity in each NMA.

The analysis of change from baseline in DT count was conducted in the subgroup of patients with at least one DT at baseline. To allow comparisons with the secukinumab trials, NRS30 skin pain response was defined as follows in the BE HEARD trials: a ≥ 30% reduction and reduction of ≥ 2 units from baseline in Worst Skin Pain HSSDD of Skin Pain, assessed in patients with a baseline HSSDD score of ≥ 3. The same response thresholds and patient

subpopulation were used in the SUNRISE/SUNSHINE trials to define NRS30; however, the Patient's Global Assessment of Skin Pain was used to measure skin pain in SUNRISE/SUNSHINE.

For the subgroup of biologic-experienced patients at week 16, an NMA assessing HiSCR50 (mNRI for HS-ABX) and an NMA assessing percentage change in AN count (MI for HS-ABX) were also conducted.

The HiSCR50, HiSCR75 and HiSCR90 results from the NMA feed into the economic model described in section B.3, providing evidence for the cost-effectiveness of bimekizumab versus secukinumab.

B.2.9.1 Evidence for network meta-analysis

Table 37 summarises the relevant interventions and studies included in the NMA. The evidence network for the NMA of overall trial populations is shown in Figure 19. The NMA could be conducted only at week 12–16; it was not possible to construct a connected treatment network at later timepoints due to the lack of placebo comparator in the BE HEARD and SUNRISE/SUNSHINE trials after the initial treatment period. For the NMA of biologic-experienced patients, only BE HEARD trial data and pooled SUNRISE/SUNSHINE trial data were available (Appendix D.1.5.3, Figure 39).

Table 37 Summary of relevant interventions and studies included in NMA

Study arm	Studies with this arm
Bimekizumab 320 mg Q2W	HS0001 [116], BE HEARD I [113, 115], BE HEARD II [114, 115]
Bimekizumab 320 mg Q4W	BE HEARD I [113, 115], BE HEARD II [114, 115]
Secukinumab 300 mg Q2W [a]	SUNRISE [48], SUNSHINE [48]
Secukinumab 300 mg Q4W	SUNRISE [48], SUNSHINE [48]
Placebo	All studies listed above plus four adalimumab trials: [b] PIONEER I [46], PIONEER II [46], NCT00918255 [149], SHARPS [109]

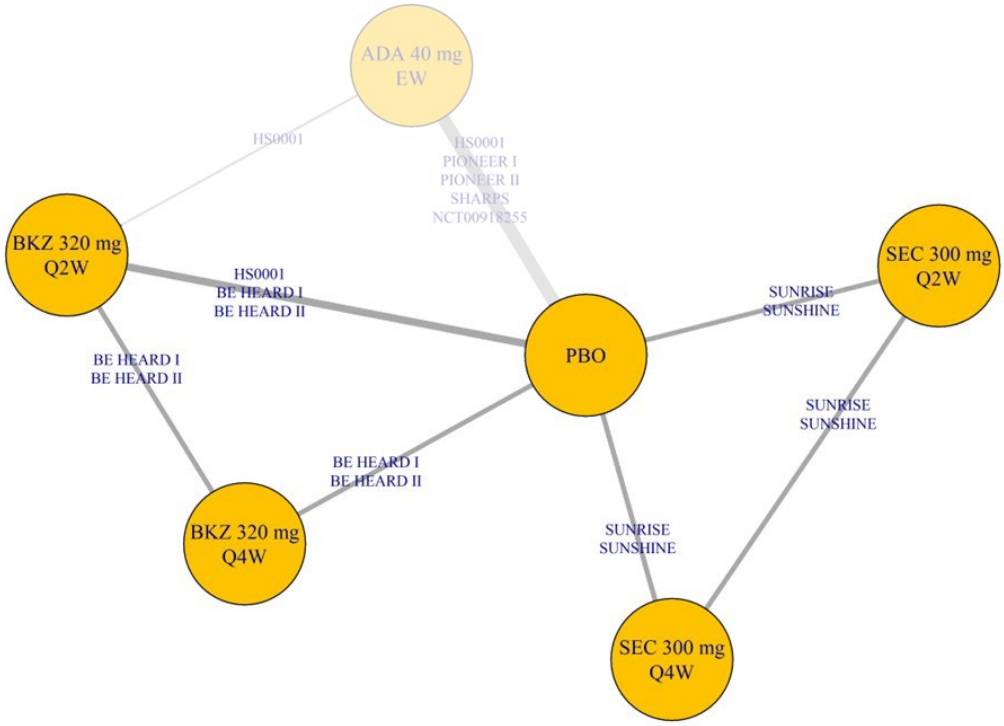
[a] Only recommended for non-responders after week 16–28, which is outside the timepoint of interest for the NMA.
[b] Although some outcome networks did include adalimumab, the NMA results for adalimumab are not presented here as a comparison with adalimumab is not considered within scope (explained further in section B.1.1). More comprehensive NMA results (including adalimumab) are presented in Appendix D.1.5.6.
NMA, network meta-analysis; Q2W, every two weeks; Q4W, every four weeks.

B.2.9.2 Network meta-analysis results

B.2.9.2.1 Model selection

The fixed-effect, placebo-adjusted model was selected for HiSCR50, HiSCR75, HiSCR90 and HiSCR100 analyses, and the fixed-effect model without adjustment was selected for the analyses of HiSCR50 among biologic-experienced patients, IHS4-55, IHS4 change from baseline, percent change in AN count, absolute change in DT count and skin pain response. The model selection process is described in detail in Appendix D.1.5.5 and was based on several factors including model goodness of fit statistics and an assessment of correlation between placebo response and treatment effect. Additionally, placebo-adjusted models could not be run for some outcomes due to limited reporting. Results for additional models are summarised in Appendix D.1.5.7, Table 110 and Table 111.

Figure 19 NMA evidence network at weeks 12–16



Adalimumab is greyed out in the evidence network as, although these trials were included in the NMA when relevant outcome data were reported, a comparison with adalimumab is not considered within scope (explained further in section B.1.1). More comprehensive NMA results (including adalimumab) are presented in Appendix D.1.5.6.

ADA, adalimumab; BKZ, bimekizumab; EW, every week; PBO, placebo; QW, every week; Q2W, once every two weeks; Q4W, once every four weeks; SEC, secukinumab.

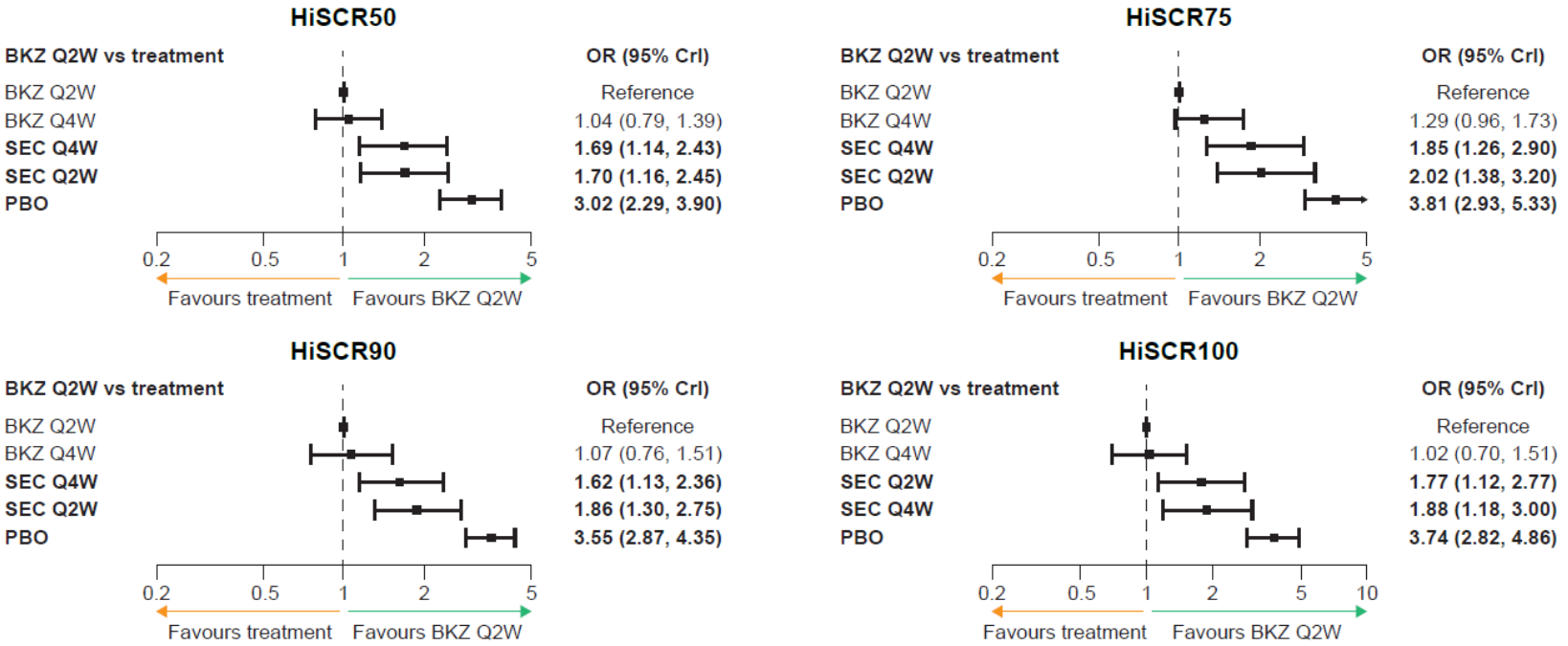
Treatment outcome data included in the NMA analyses are shown in Appendix D.1.4.4, Tables 91–101.

B.2.9.2.2 HiSCR50, HiSCR75, HiSCR90 and HiSCR100 at week 16

The results of the NMAs assessing HiSCR50, HiSCR75, HiSCR90 and HiSCR100 in the overall population are shown in Figure 20 and Table 38. Patients treated with any of the active treatments had statistically significantly higher odds of achieving HiSCR50, HiSCR75, HiSCR90 and HiSCR100 at week 16, compared to placebo.

Patients treated with bimekizumab 320 mg Q2W had higher odds of achieving all response thresholds compared with all other active treatments at week 16. These comparisons were statistically significant versus secukinumab 300 mg Q2W and Q4W for all four HiSCR thresholds (OR [95% credible interval; CrI] for bimekizumab 320 mg Q2W vs secukinumab 300 mg Q2W: HiSCR50, 1.70 [1.16–2.45]; HiSCR75, 2.02 [1.38–3.20]; HiSCR90, 1.86 [1.30–2.75]; HiSCR100, 1.77 [1.12–2.77]). In all four comparisons, bimekizumab 320 mg Q2W had the highest probability of being ranked as the most effective treatment and bimekizumab 320 mg Q4W had the second highest probability (based on the proportion of the 10,000 simulations run in which bimekizumab 320 mg Q2W was the most effective therapy; Table 38).

Figure 20 Forest plots of week 16 HiSCR50, HiSCR75, HiSCR90 and HiSCR100 NMA results: bimekizumab 320 mg Q2W vs other treatments (mNRI for HS-ABX; fixed-effect model with placebo adjustment)



mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.

ABX, antibiotics; BKZ, bimekizumab; CrI, credible interval; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; OR, odds ratio; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab.

Table 38 Week 16 NMA results for HiSCR50, HiSCR75, HiSCR90 and HiSCR100 (mNRI for HS-ABX; fixed-effect model with placebo adjustment)

		PBO	BKZ 320 mg Q2W	BKZ 320 mg Q4W	SEC 300 mg Q2W	SEC 300 mg Q4W
HiSCR50	Trt vs PBO; OR (95% CrI)	Reference	**3.02 (2.29–3.90)**	**2.90 (2.08–3.99)**	**1.78 (1.33–2.38)**	**1.79 (1.34–2.40)**
	Trt vs PBO; RR (95% CrI)	Reference	**1.87 (1.64–2.09)**	**1.83 (1.56–2.10)**	**1.44 (1.21–1.68)**	**1.44 (1.22–1.68)**
	BKZ Q2W vs Trt; OR (95% CrI)	**3.02 (2.29–3.90)**	Reference	1.04 (0.79–1.39)	**1.70 (1.16–2.45)**	**1.69 (1.14–2.43)**
	BKZ Q2W vs Trt; RR (95% CrI)	**1.87 (1.64–2.09)**	Reference	1.02 (0.90–1.16)	**1.30 (1.07–1.57)**	**1.30 (1.07–1.56)**
	Absolute response (95% CrI)	30.5% (27.7–33.5%)	57.0% (49.3–63.8%)	56.0% (47.0–64.3%)	43.9% (36.1–51.8%)	44.0% (36.4–52.1%)
	Rank 1, % of simulations	0.0%	57.1%	36.2%	0.3%	0.3%
HiSCR75	Trt vs PBO; OR (95% CrI)	Reference	**3.81 (2.93–5.33)**	**2.96 (2.13–4.36)**	**1.88 (1.39–2.52)**	**2.06 (1.53–2.77)**
	Trt vs PBO; RR (95% CrI)	Reference	**2.68 (2.27–3.25)**	**2.29 (1.82–2.91)**	**1.66 (1.31–2.06)**	**1.78 (1.42–2.19)**
	BKZ Q2W Vs Trt; OR (95% CrI)	**3.81 (2.93–5.33)**	Reference	1.29 (0.96–1.73)	**2.02 (1.38–3.20)**	**1.85 (1.26–2.90)**
	BKZ Q2W Vs Trt; RR (95% CrI)	**2.68 (2.27–3.25)**	Reference	1.17 (0.98–1.43)	**1.61 (1.24–2.19)**	**1.51 (1.17–2.03)**
	Absolute response (95% CrI)	14.9% (12.7–17.5%)	40.1% (32.7–49.4%)	34.2% (26.2–44.4%)	24.8% (18.8–31.9%)	26.6% (20.3–33.9%)
	Rank 1, % of simulations	0.0%	94.4%	4.3%	0.1%	0.3%
HiSCR90	Trt vs PBO; OR (95% CrI)	Reference	**3.55 (2.87–4.35)**	**3.32 (2.45–4.43)**	**1.90 (1.37–2.57)**	**2.19 (1.61–2.93)**
	Trt vs PBO; RR (95% CrI)	Reference	**2.99 (2.53–3.53)**	**2.84 (2.21–3.57)**	**1.78 (1.34–2.31)**	**2.02 (1.54–2.58)**
	BKZ Q2W Vs Trt; OR (95% CrI)	**3.55 (2.87–4.35)**	Reference	1.07 (0.76–1.51)	**1.86 (1.30–2.75)**	**1.62 (1.13–2.36)**
	BKZ Q2W Vs Trt; RR (95% CrI)	**2.99 (2.53–3.53)**	Reference	1.05 (0.80–1.39)	**1.68 (1.24–2.34)**	**1.48 (1.10–2.04)**
	Absolute response (95% CrI)	7.2% (5.6–9.1%)	21.5% (16.3–27.8%)	20.5% (14.6–27.5%)	12.8% (8.9–18.1%)	14.5% (10.2–20.1%)
	Rank 1, % of simulations	0.0%	64.3%	35.1%	0.0%	0.2%
HiSCR100	Trt vs PBO; OR (95% CrI)	Reference	**3.74 (2.82, 4.86)**	**3.66 (2.52, 5.14)**	**2.12 (1.45, 3.02)**	**2.00 (1.35, 2.86)**
	Trt vs PBO; RR (95% CrI)	Reference	**3.29 (2.57, 4.11)**	**3.23 (2.34, 4.28)**	**2.01 (1.42, 2.75)**	**1.90 (1.32, 2.63)**
	BKZ Q2W Vs Trt; OR (95% CrI)	**3.74 (2.82, 4.86)**	Reference	1.02 (0.70, 1.51)	**1.77 (1.12, 2.77)**	**1.88 (1.18, 3.00)**
	BKZ Q2W Vs Trt; RR (95% CrI)	**3.29 (2.57, 4.11)**	Reference	1.02 (0.74, 1.41)	**1.64 (1.10, 2.45)**	**1.73 (1.16, 2.64)**
	Absolute response (95% CrI)	4.90% (3.4–7.1%)	16.2% (10.5–23.7%)	15.9% (9.8–24.2%)	9.9% (6.0–15.8%)	9.3% (5.6–15.0%)
	Rank 1, % of simulations	0.0%	40.8%	35.6%	0.4%	0.3%

Statistically significant results are highlighted in **bold**.

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.

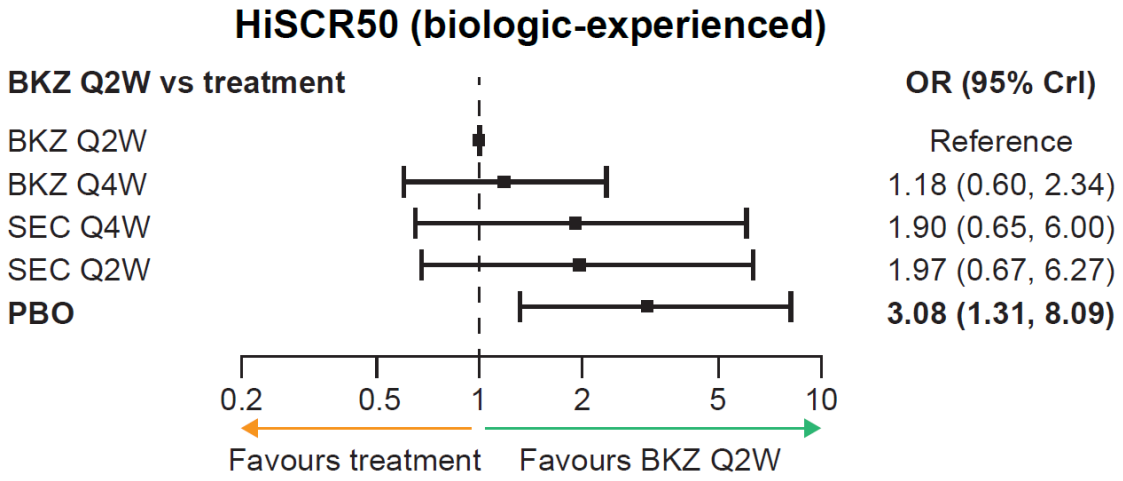
Percentages for rank 1 data do not add up to 100% due to exclusion of adalimumab; see full tables in Appendix D.1.5.6.

ABX, antibiotics; BKZ, bimekizumab; CrI, credible interval; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; OR, odds ratio; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; trt, treatment.

B.2.9.2.3 HiSCR50 among biologic-experienced patients at week 16

NMA results for the biologic-experienced subgroup at week 16 are shown in Figure 21 and Table 39. The point estimates for the week 16 ORs were higher for bimekizumab 320 mg Q2W versus secukinumab 300 mg Q2W and Q4W than in the base analysis. However, the 95% credible intervals were wider, most likely due to the small sample sizes in the trial subgroups (OR [95% CrI] for bimekizumab 320 mg Q2W vs secukinumab 300 mg Q2W: 1.97 [0.67–6.27]). The only statistically significant difference in efficacy was between bimekizumab 320 mg Q2W and placebo. Bimekizumab 320 mg Q2W had the highest probability of being the most effective treatment (59.1%, vs 6.0% and 7.2% for secukinumab 300 mg Q2W and Q4W, respectively) and bimekizumab 320 mg Q4W had the second highest probability.

Figure 21 Forest plot of week 16 HiSCR50 NMA results among biologic-experienced patients: bimekizumab 320 mg Q2W vs other treatments (mNRI for HS-ABX; fixed-effect model)



mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
ABX, antibiotics; BKZ, bimekizumab; CrI, credible interval; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; OR, odds ratio; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab.

Table 39 Week 16 NMA results for HiSCR50 among biologic-experienced patients (mNRI for HS-ABX; fixed-effect model)

	PBO	BKZ 320 mg Q2W	BKZ 320 mg Q4W	SEC 300 mg Q2W	SEC 300 mg Q4W
Trt vs PBO; OR (95% CrI)	Reference	**3.08 (1.31–8.09)**	2.62 (0.99–7.58)	1.57 (0.82–3.01)	1.63 (0.86–3.10)
Trt vs PBO; RR (95% CrI)	Reference	**1.94 (1.20–2.85)**	1.80 (0.99–2.77)	1.35 (0.86–1.95)	1.38 (0.89–1.98)
BKZ Q2W vs Trt; OR (95% CrI)	**3.08 (1.31–8.09)**	Reference	1.18 (0.60–2.34)	1.97 (0.67–6.27)	1.90 (0.65–6.00)
BKZ Q2W vs Trt; RR (95% CrI)	**1.94 (1.20–2.85)**	Reference	1.08 (0.79–1.59)	1.43 (0.80–2.60)	1.40 (0.78–2.51)
Absolute response (95% CrI)	27.7% (20.5–36.2%)	54.1% (31.4–76.9%)	50.0% (26.0–75.5%)	37.5% (22.0–56.0%)	38.4% (22.6–57.0%)
Rank 1, % of simulations	0.0%	59.1%	27.7%	6.0%	7.2%

Statistically significant results are highlighted in **bold**.
mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
Percentages for rank 1 data do not add up to 100% due to exclusion of adalimumab; see full tables in Appendix D.1.5.6.
ABX, antibiotics; BKZ, bimekizumab; CrI, credible interval; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; OR, odds ratio; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; trt, treatment.

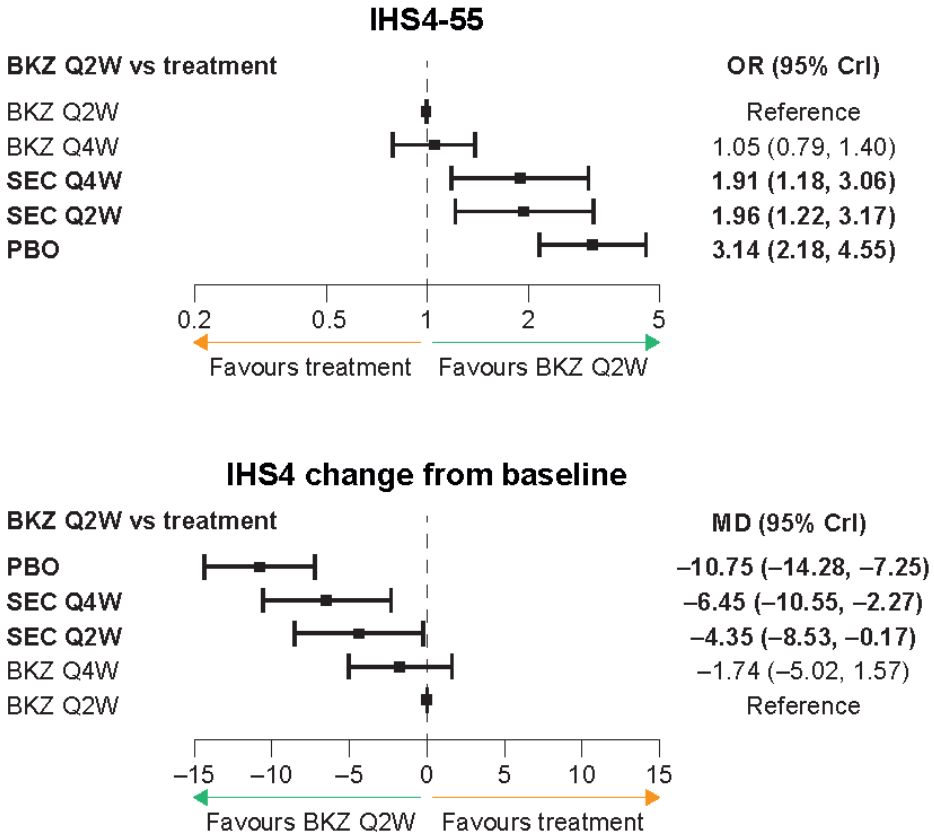
B.2.9.2.4 IHS4 outcomes at week 16

The results of the NMAs assessing week 16 IHS4 outcomes in the overall population are shown in Table 40. Patients treated with bimekizumab 320 mg Q2W had statistically significantly higher odds of achieving IHS4-55 at week 16, compared with secukinumab 300 mg Q2W and Q4W (OR [95% CrI] vs secukinumab Q2W: 1.96 [1.22–3.17]; Figure 22).

In the analysis of IHS4 change from baseline, bimekizumab 320 mg Q2W had a statistically significantly higher mean improvement than secukinumab 300 mg Q2W and Q4W (mean difference [95% CrI] vs secukinumab 300 mg Q2W, −4.35 [−8.53, −0.17]; vs secukinumab 300 mg Q4W, −6.45 [−10.55, −2.27]; Figure 22).

For both IHS4 outcomes, bimekizumab 320 mg Q2W had the highest probability of being ranked as the most effective treatment and bimekizumab 320 mg Q4W had the second highest probability (Table 40).

Figure 22 Forest plots of week 16 IHS4 NMA results (mNRI for HS-ABX; MI for HS-ABX; fixed-effect model)



mNRI for HS-ABX (IHS4-55): patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to an AE or lack of efficacy are treated as non-responders at all subsequent visits.
MI for HS-ABX (IHS4 change from baseline): Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to an AE or lack of efficacy were treated as missing at all subsequent visits.
ABX, antibiotics; BKZ, bimekizumab; CrI, credible interval; HS, hidradenitis suppurativa; MD, mean difference; MI, multiple imputation; mNRI, modified non-responder imputation; OR, odds ratio; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab.

Table 40 Week 16 NMA results for IHS4-55 (mNRI for HS-ABX) and IHS4 change from baseline (MI for HS-ABX; fixed-effect model)

		PBO	BKZ 320 mg Q2W	BKZ 320 mg Q4W	SEC 300 mg Q2W	SEC 300 mg Q4W
IHS4-55	**Trt vs PBO; OR (95% CrI)**	Reference	**3.14 (2.18–4.55)**	**2.98 (1.99–4.52)**	**1.60 (1.18–2.18)**	**1.65 (1.22–2.24)**
	Trt vs PBO; RR (95% CrI)	Reference	**1.85 (1.57–2.15)**	**1.82 (1.50–2.14)**	**1.34 (1.11–1.58)**	**1.36 (1.14–1.60)**
	BKZ Q2W vs Trt; OR (95% CrI)	**3.14 (2.18–4.55)**	Reference	1.05 (0.79–1.40)	**1.96 (1.22–3.17)**	**1.91 (1.18–3.06)**
	BKZ Q2W vs Trt; RR (95% CrI)	**1.85 (1.57–2.15)**	Reference	1.02 (0.91–1.16)	**1.38 (1.10–1.75)**	**1.36 (1.08–1.71)**
	Absolute response (95% CrI)	32.3% (28.4–36.4%)	60.0% (50.0–69.4%)	58.7% (47.6–69.1%)	43.3% (34.9–52.3%)	44.0% (35.5–52.9%)
	Rank 1, % of simulations	0.0%	45.7%	27.4%	0.0%	0.0%
IHS4 CfB	**Trt vs PBO; MD (95% CrI)**	Reference	**−10.75 (−14.28, −7.25)**	**−9.02 (−13.06, −5.09)**	**−6.41 (−8.68, −4.17)**	**−4.32 (−6.54, −2.11)**
	BKZ Q2W vs Trt; MD (95% CrI)	**−10.75 (−14.28, −7.25)**	Reference	−1.74 (−5.02, 1.57)	**−4.35 (−8.53, −0.17)**	**−6.45 (−10.55, −2.27)**
	Absolute CFB; MD (95% CrI)	−5.3 (−6.8, −3.9)	−16.1 (−19.9, −12.3)	−14.4 (−18.6, −10.2)	−11.8 (−14.4, −9.1)	−9.7 (−12.3, −7.0)
	Rank 1, % of simulations	0.0%	83.2%	15.1%	1.7%	0.0%

Statistically significant results are highlighted in **bold**.

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.

MI for HS-ABX: Participants who experienced an intercurrent event were treated as missing following the intercurrent event. Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as missing at all subsequent visits.

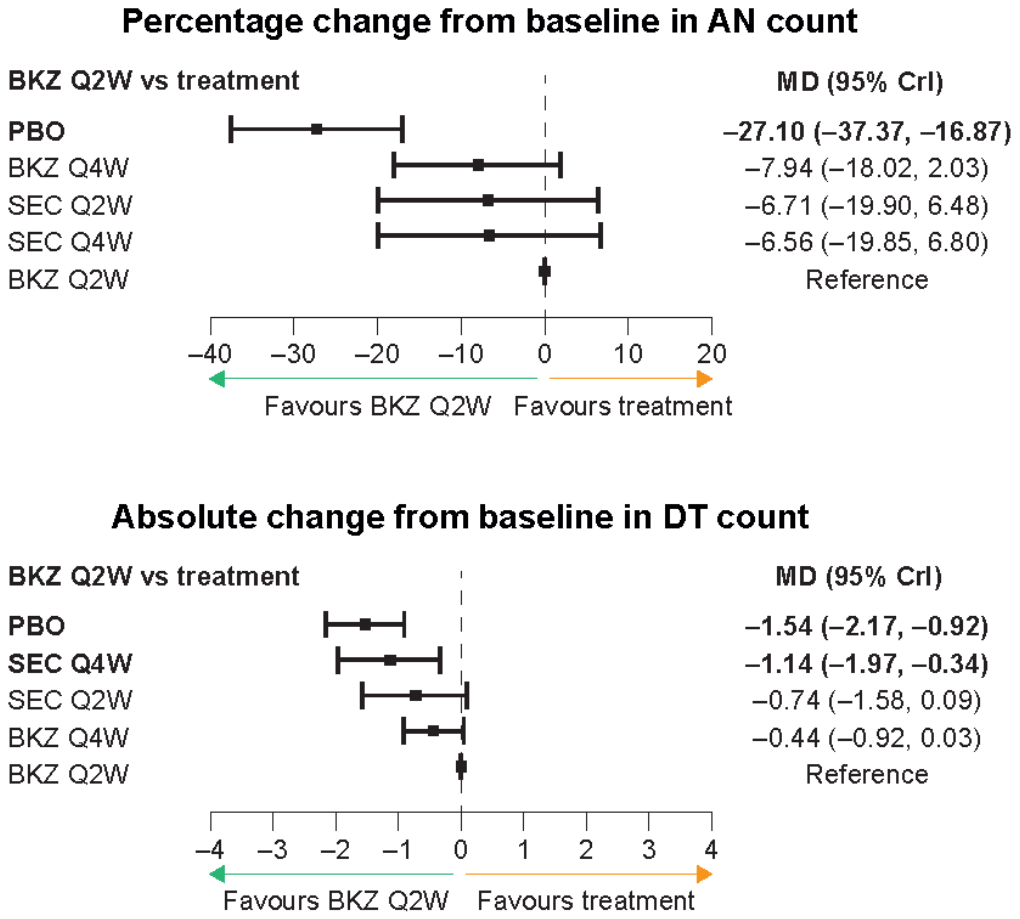
Percentages for rank 1 data do not add up to 100% due to exclusion of adalimumab; see full tables in Appendix D.1.5.6.

ABX, antibiotics; BKZ, bimekizumab; CfB, change from baseline; CrI, credible interval; HS, hidradenitis suppurativa; IHS4, International Hidradenitis Suppurativa Severity Score System; MD, mean difference; MI, multiple imputation; mNRI, modified non-responder imputation; OR, odds ratio; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; trt, treatment.

B.2.9.2.5 Mean percentage change from baseline in AN count at week 16

The results of the NMA assessing percentage change from baseline in AN count (see section B.2.3.1.6, Table 9) for the overall population are shown in Figure 23 and Table 41. Patients treated with any of the active treatments experienced significantly larger mean percentage reductions in AN count, compared with placebo. Patients treated with bimekizumab 320 mg Q2W had numerically larger mean percentage reductions in AN count at week 16, compared with all other treatments, with bimekizumab 320 mg Q2W having the highest estimated probability of being ranked the best treatment (49.7%).

Figure 23 Forest plot of week 16 percentage change from baseline in AN count NMA results (MI for HS-ABX; fixed-effect model)



MI for HS-ABX: Participants who experienced an intercurrent event were treated as missing following the intercurrent event. Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as missing at all subsequent visits.ABX, antibiotics; AN, abscess and inflammatory nodule; BKZ, bimekizumab; CrI, credible interval; HS, hidradenitis suppurativa; MD, mean difference; MI, multiple imputation; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; trt, treatment.

Table 41 Week 16 NMA results for percentage change from baseline in AN count (MI for HS-ABX; fixed-effect model)

	PBO	BKZ Q2W	BKZ Q4W	SEC Q2W	SEC Q4W
Trt vs PBO; MD % change (95% CrI)	Reference	**−27.10 (−37.37, −16.87)**	**−19.14 (−31.90, −6.61)**	**−20.37 (−28.47, −12.34)**	**−20.51 (−28.96, −12.12)**
BKZ Q2W vs trt; MD % change (95% CrI)	**−27.10 (−37.37, −16.87)**	Reference	−7.94 (−18.02, 2.03)	−6.71 (-19.90, 6.48)	−6.56 (−19.85, 6.80)
Absolute change (95% CrI)	−24.3 (−29.4, −19.2)	−51.5 (−62.8, −40.0)	−43.5 (−57.1, −30.0)	−44.7 (−54.3, −35.1)	−44.8 (−54.7, −35.0)
Rank 1, % of simulations	0.0%	49.7%	3.1%	4.7%	5.1%

Statistically significant results are highlighted in **bold**.

MI for HS-ABX: Participants who experienced an intercurrent event were treated as missing following the intercurrent event. Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as missing at all subsequent visits.

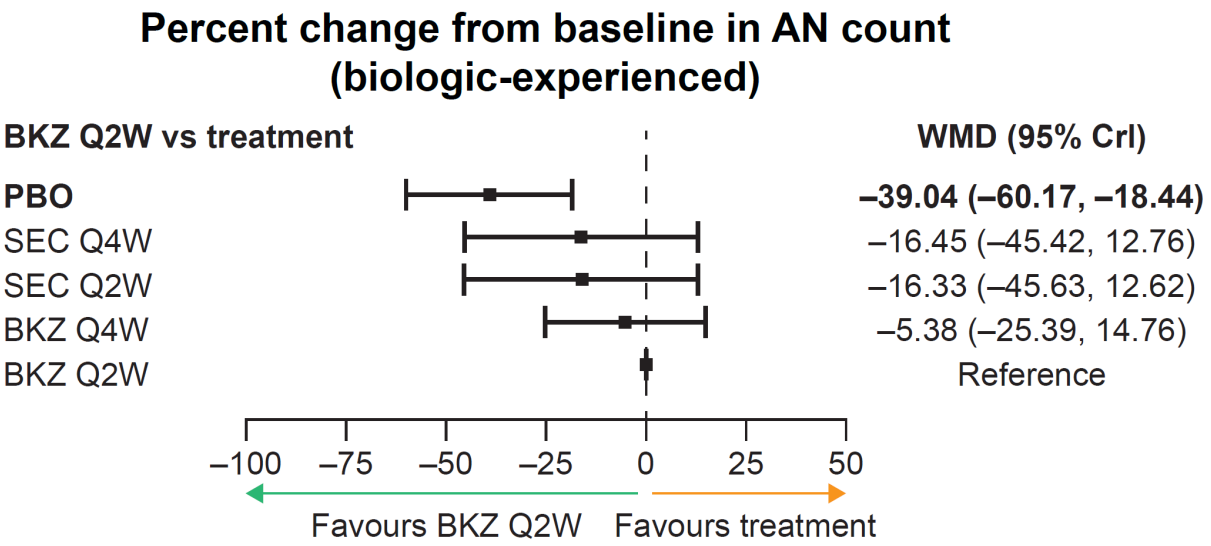
Percentages for rank 1 data do not add up to 100% due to exclusion of adalimumab; see full tables in Appendix D.1.5.6.

ABX, antibiotics; AN, abscess and inflammatory nodule; BKZ, bimekizumab; CrI, credible interval; HS, hidradenitis suppurativa; MD, mean difference; MI, multiple imputation; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; trt, treatment.

B.2.9.2.6 Mean percentage change in AN count among biologic-experienced patients

The results of the NMA assessing percentage change from baseline in AN count (see section B.2.3.1.6, Table 9) among biologic-experienced patients are shown in Figure 24 and Table 42. Patients treated with bimekizumab 320 mg Q2W had numerically larger mean percentage reductions in AN count at week 16, compared with secukinumab 300 mg Q2W (mean difference [95% CrI], −16.33% [−45.63%, 12.62%]) and secukinumab 300 mg Q4W (mean difference, −16.45% [−45.42%, 12.76%]). Bimekizumab 320 mg Q2W had the highest estimated probability of being ranked the best treatment (57.5%).

Figure 24 Forest plot of week 16 percentage change from baseline in AN count NMA results among biologic-experienced patients (MI for HS-ABX; fixed-effect model)



MI for HS-ABX: Participants who experienced an intercurrent event were treated as missing following the intercurrent event. Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as missing at all subsequent visits.

ABX, antibiotics; AN, abscess and inflammatory nodule; BKZ, bimekizumab; CrI, credible interval; HS, hidradenitis suppurativa; MD, mean difference; MI, multiple imputation; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; trt, treatment.

Table 42 Week 16 NMA results for percentage change from baseline in AN count among biologic-experienced patients (MI for HS-ABX; fixed-effect model)

	PBO	BKZ Q2W	BKZ Q4W	SEC Q2W	SEC Q4W
Trt vs PBO; MD % change (95% CrI)	Reference	**−39.04 (−60.17, −18.44)**	**−33.72 (−59.89, −8.09)**	**−22.74 (−43.01, −2.63)**	**−22.79 (−43.13, −2.50)**
BKZ Q2W vs trt; MD % change (95% CrI)	**−39.04 (−60.17, −18.44)**	Reference	−5.38 (−25.39, 14.76)	−16.33 (−45.63, 12.62)	−16.45 (−45.42, 12.76)
Absolute change (95% CrI)	−16.5 (−28.6, −4.2)	−55.5 (−79.9, −31.7)	−50.2 (−78.8, −21.8)	−39.2 (−62.8, −15.5)	−39.2 (−62.8, −15.7)
Rank 1, % of simulations	0.0%	57.5%	26.0%	8.1%	8.4%

Statistically significant results are highlighted in **bold**. Percentages for rank 1 data do not add up to 100% due to exclusion of adalimumab; see full tables in Appendix D.1.5.6.

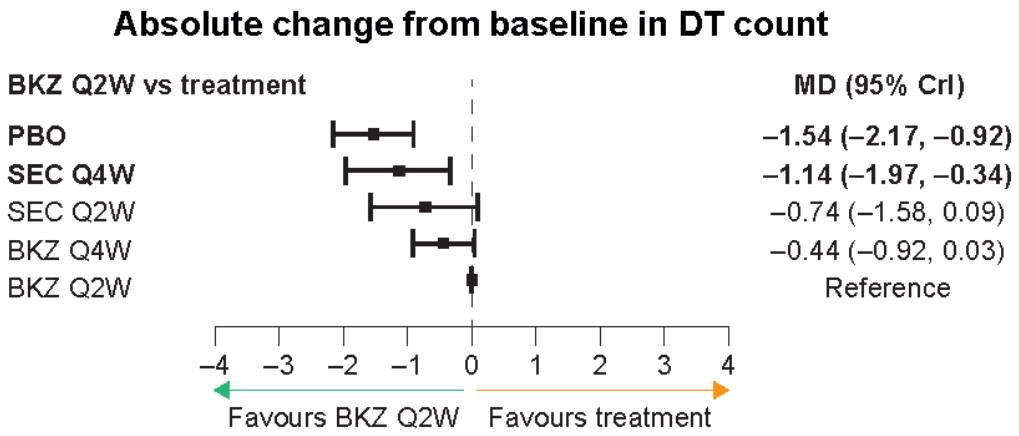
MI for HS-ABX: Participants who experienced an intercurrent event were treated as missing following the intercurrent event. Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as missing at all subsequent visits. ABX, antibiotics; AN, abscess and inflammatory nodule; BKZ, bimekizumab; CrI, credible interval; HS, hidradenitis suppurativa; MD, mean difference; MI, multiple imputation; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; trt, treatment.

B.2.9.2.7 Mean change from baseline in draining tunnel count at week 16

The results of the NMA assessing absolute change from baseline in DT count (among patients with at least one draining tunnel at baseline) are shown in Figure 25 and Table 43. All of the active treatments were associated with larger reductions in DT count than placebo.

Patients treated with bimekizumab 320 mg Q2W had a numerically larger mean reduction in DT count at week 16, compared with all other treatments; the difference was statistically significant compared with secukinumab 300 mg Q4W (mean difference [95% CrI], −1.14% [−1.97%, −0.34%]). Bimekizumab 320 mg Q2W had the highest estimated probability of being ranked the best treatment (80.1%, vs 3.1% for secukinumab 300 mg Q2W).

Figure 25 Forest plot of week 16 absolute change from baseline in draining tunnel count NMA results (MI for HS-ABX; fixed-effect model)



MI for HS-ABX: Participants who experienced an intercurrent event were treated as missing following the intercurrent event. Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as missing at all subsequent visits. ABX, antibiotics; BKZ, bimekizumab; CrI, credible interval; DT, draining tunnel; HS, hidradenitis suppurativa; MD, mean difference; MI, multiple imputation; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; trt, treatment.

Table 43 Week 16 NMA results for absolute change from baseline in draining tunnel count (MI for HS-ABX; fixed-effect model)

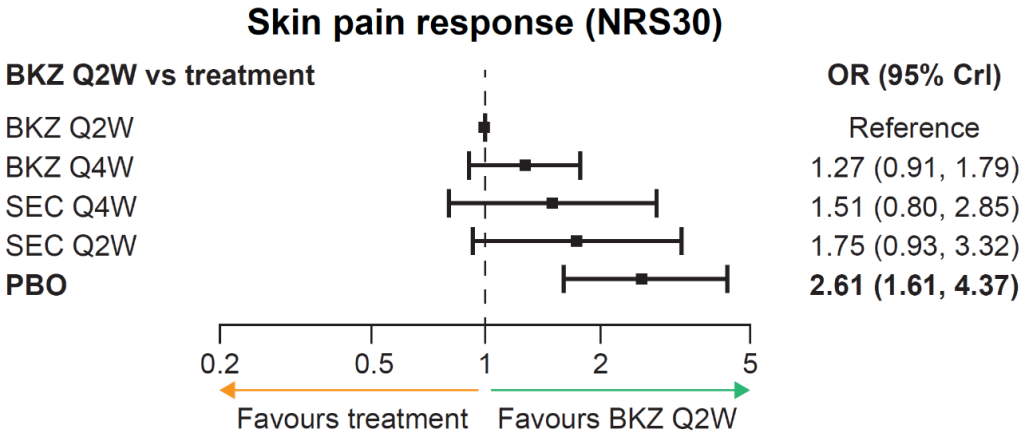
	PBO	BKZ Q2W	BKZ Q4W	SEC Q2W	SEC Q4W
Trt vs PBO; MD change (95% CrI)	Reference	**−1.54 (−2.17, −0.92)**	**−1.10 (−1.77, −0.46)**	**−0.80 (−1.34, −0.25)**	−0.40 (−0.92, 0.13)
BKZ Q2W vs trt; MD change (95% CrI)	**−1.54 (−2.17, −0.92)**	Reference	−0.44 (−0.92, 0.03)	−0.74 (−1.58, 0.09)	**−1.14 (−1.97, −0.34)**
Absolute change (95% CrI)	−0.8 (−1.1, −0.4)	−2.3 (−3.0, −1.6)	−1.9 (−2.6, −1.1)	−1.6 (−2.2, −0.9)	−1.2 (−1.8, −0.5)
Rank 1, % of simulations	0.0%	80.1%	2.7%	3.1%	0.1%

Statistically significant results are highlighted in **bold**.
MI for HS-ABX: Participants who experienced an intercurrent event were treated as missing following the intercurrent event. Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as missing at all subsequent visits.
Percentages for rank 1 data do not add up to 100% due to exclusion of adalimumab; see full tables in Appendix D.1.5.6. ABX, antibiotics; BKZ, bimekizumab; CrI, credible interval; HS, hidradenitis suppurativa; MD, mean difference; MI, multiple imputation; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; trt, treatment.

B.2.9.2.8 Skin pain response at week 16

Week 16 skin pain response outcomes in the NMA, using the NRS30 definition, are shown in Figure 26 and Table 44. Patients treated with any of the active treatments had statistically significantly higher odds of achieving an NRS30 response, compared with placebo. Patients treated with bimekizumab 320 mg Q2W had higher odds of achieving an NRS30 response at week 16, compared with either secukinumab regimen, but the differences were not statistically significant (OR [95% CrI] for bimekizumab 320 mg Q2W vs secukinumab 300 mg Q2W: 1.51 [0.80, 2.85]). However, bimekizumab 320 mg Q2W had the highest probability of being ranked as the most effective treatment (82.5% of simulations, compared with 8.8% and 1.8% for secukinumab 300 mg Q2W and Q4W, respectively).

Figure 26 Forest plot of week 16 NRS30 skin pain response NMA results (mNRI for HS-ABX; fixed-effect model)



mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
NRS30 (for BE HEARD trials): ≥ 30% reduction and reduction of ≥ 2 units from baseline in HSSDD weekly worst skin pain NRS score, assessed in patients with a baseline HSSDD score of ≥ 3.
ABX, antibiotics; BKZ, bimekizumab; CrI, credible interval; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; NRS, numerical rating scale; OR, odds ratio; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; trt, treatment.

Table 44 Week 16 NMA results for skin pain response (NRS30; mNRI for HS-ABX; fixed-effect model)

	PBO	BKZ Q2W	BKZ Q4W	SEC Q2W	SEC Q4W
Trt vs PBO; OR (95% CrI)	Reference	**2.61 (1.61, 4.37)**	**2.05 (1.22, 3.55)**	**1.74 (1.17, 2.59)**	**1.50 (1.00, 2.24)**
Trt vs PBO; RR (95% CrI)	Reference	**1.82 (1.38, 2.32)**	**1.60 (1.15, 2.12)**	**1.45 (1.12, 1.82)**	**1.32 (1.00, 1.69)**
BKZ Q2W Vs Trt; OR (95% CrI)	**2.61 (1.61, 4.37)**	Reference	1.27 (0.91, 1.79)	1.51 (0.80, 2.85)	1.75 (0.93, 3.32)
BKZ Q2W Vs Trt; RR (95% CrI)	**1.82 (1.38, 2.32)**	Reference	1.14 (0.95, 1.39)	1.26 (0.88, 1.77)	1.38 (0.96, 1.98)
Absolute response (95% CrI)	26.9% (22.4%, 32.0%)	49.1% (36.1%, 63.1%)	43.1% (29.9%, 58.0%)	39.0% (28.8%, 50.6%)	35.6% (25.8%, 47.1%)
Rank 1, % of simulations	0.0%	82.5%	6.8%	8.8%	1.8%

Statistically significant results are highlighted in **bold**. mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits. Percentages for rank 1 data do not add up to 100% due to exclusion of adalimumab; see full tables in Appendix D.1.5.6.

NRS30 (for BE HEARD trials): ≥ 30% reduction and reduction of ≥ 2 units from baseline in HSSDD weekly worst skin pain NRS score, assessed in patients with a baseline HSSDD score of ≥ 3.

ABX, antibiotics; BKZ, bimekizumab; CrI, credible interval; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; NRS, numerical rating scale; OR, odds ratio; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; trt, treatment.

B.2.9.3 MAIC methodology and included trials

For the analysis of data after week 16, an NMA was infeasible as it was not possible to construct a connected treatment network between the bimekizumab and secukinumab trials due to the lack of placebo arms after the initial treatment periods. Given this, an unanchored MAIC utilising data from the BE HEARD (week 48) and SUNRISE/SUNSHINE (week 52) trials was conducted.

Details of the MAIC methodology are reported in Appendix D.1.6. Table 45 summarises the treatment arms included in the MAIC analysis. Outcomes assessed using MAIC analysis and reported in this submission were HiSCR50, HiSCR75 and HiSC90. To account for differences in discontinuation rates, and given that baseline characteristics were not reported for the OC cohort for the pooled SUNRISE and SUNSHINE dataset at week 48, the NRI estimand was used for all MAIC analyses reported in this section.

The approved secukinumab maintenance regimen is 300 mg monthly; based on clinical response, this can be increased to 300 mg every 2 weeks [103]. Accordingly, both the Q2W and Q4W doses of secukinumab from the SUNRISE and SUNSHINE trials were included in the MAIC.

Table 45 Summary of study arms included in MAIC

Study arm	Studies with this arm
Bimekizumab 320 mg Q2W/Q4W	Pooled BE HEARD trials [115]
Secukinumab 300 mg Q2W	Pooled SUNRISE and SUNSHINE [48]
Secukinumab 300 mg Q4W	Pooled SUNRISE and SUNSHINE [48]

MAIC, matching-adjusted indirect comparison; QW, every week; Q2W, every two weeks; Q4W, every four weeks.

The MAIC was adjusted for sex (% male), race (% white), age, BMI, duration of HS, smoking (% current smokers), severity (% Hurley III), region (% US), DT count, abscess and inflammatory nodules count, prior biologics (%) and concomitant antibiotics (%).

B.2.9.4 MAIC results for bimekizumab 320 mg Q2W/Q4W vs secukinumab 300 mg Q2W and Q4W

Matching results

As shown in Appendix D.1.6.2 (Table 112 and Table 113), the matching process applied to the pooled BE HEARD bimekizumab 320 mg Q2W/Q4W arm successfully replicated the pooled SUNRISE/SUNSHINE average baseline characteristics of the relevant secukinumab arms. The effective sample size (ESS) was 226 (77.4% of the sample size before matching) for the comparison with secukinumab 300 mg Q2W and 208 (71.2%) for the comparison with secukinumab 300 mg Q4W.

HiSCR50

The results of the MAIC assessing the proportion of patients with HiSCR50 at week 48 for bimekizumab 320 mg Q2W/Q4W versus secukinumab 300 mg Q2W and Q4W are presented in Figure 27. Compared with either secukinumab regimen, patients treated with bimekizumab 320 mg Q2W/Q4W had statistically significantly higher odds of achieving HiSCR50 at week 48 (OR [95% CI] vs secukinumab 300 mg Q2W, 2.00 [1.42–2.80]; vs secukinumab 300 mg Q4W, 2.06 [1.45–2.92]).

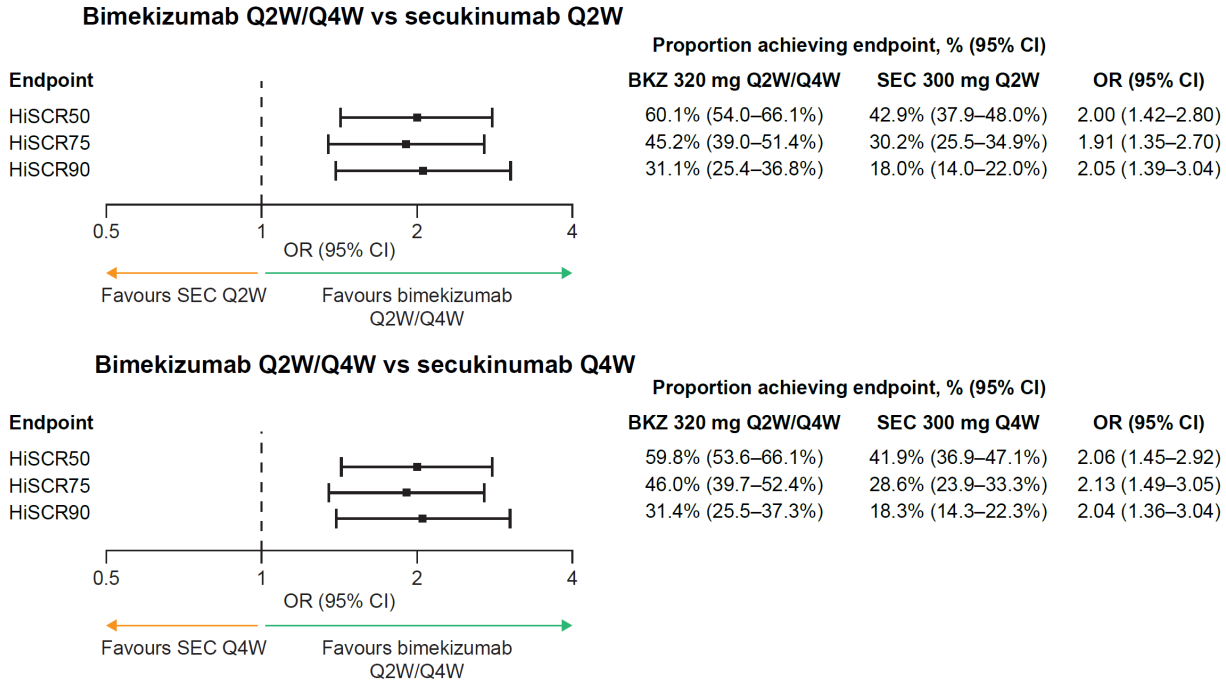
HiSCR75

Patients treated with bimekizumab 320 mg Q2W/Q4W were statistically significantly more likely to have HiSCR75 responses at week 48 than those treated with either secukinumab 300 mg Q2W (OR [95% CI], 1.91 [1.35–2.70]) or secukinumab 300 mg Q4W (OR [95% CI], 2.13 [1.49–3.05]; Figure 27).

HiSCR90

Compared with either secukinumab regimen, patients treated with bimekizumab 320 mg Q2W/Q4W had statistically significantly higher odds of achieving HiSCR50 at week 48 (OR [95% CI] vs secukinumab 300 mg Q2W, 2.05 [1.39–3.04]; vs secukinumab 300 mg Q4W, 2.04 [1.36–3.04]; Figure 27).

Figure 27 Forest plot of week 48 MAIC results for bimekizumab 320 mg Q2W/Q4W vs secukinumab 300 mg Q4W (NRI)



NRI: Missing data are imputed using NRI. Patients who have missing data at the timepoint of interest are assumed to have not responded to treatment.
The MAIC was adjusted for sex (% male), race (% white), age, BMI, duration of HS, smoking (% current smokers), severity (% Hurley III), region (% US), DT count, AN count, prior biologics (%) and concomitant antibiotics (%).
ABX, antibiotics; AN, abscess and inflammatory nodule; BKZ, bimekizumab; BMI, body mass index; CI, confidence interval; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; MAIC, matching-adjusted indirect comparison; NRI, non-responder imputation; OR, odds ratio; Q2W, every two weeks; Q4W, every four weeks; SEC, secukinumab.

B.2.9.5 Uncertainties in the indirect and mixed treatment comparisons

There was some heterogeneity observed between trials included in the NMA in terms of study design and patient baseline characteristics. Although it is normal to observe some heterogeneity within an evidence base, if there are imbalances in treatment effect modifiers then the similarity assumption may be violated.

There are some differences in clinical trial design between the adalimumab PIONEER trials and the bimekizumab BE HEARD trials; for example, the initial treatment period of the PIONEER trials was 12 weeks, whereas for the BE HEARD trials the initial treatment period was 16 weeks. Intercurrent event handling was also different between these trials (see Appendix D.1.5.4). These limitations should be taken into consideration when interpreting the results of the indirect comparison of bimekizumab versus adalimumab. However, as adalimumab is not a comparator of interest in this submission, this limitation was not considered of major relevance. Still, there may be some heterogeneity in baseline risk, given

that placebo data from all trials included in a network were used to estimate baseline risk for each analysis.

As described in sections B.2.4.3 and B.2.11, there were differences between the bimekizumab BE HEARD trial and the secukinumab trials with regard to the definition of intercurrent events relating to systemic antibiotic use. To mitigate this difference, bimekizumab data were reanalysed in a *post hoc* analysis (mNRI for HS-ABX) to match the secukinumab trial definition as closely as possible.

The lack of a placebo comparator after the initial treatment period meant that data from the clinical trials included in the NMA could not be used to compare treatment outcomes beyond 16 weeks of therapy. Instead, an unanchored MAIC was conducted as described in section B.2.9.3. Given broad similarities in study design and patient baseline characteristics across the pooled BE HEARD and pooled SUNRISE/SUNSHINE trials, the MAIC target population was believed to be reflective of the overall population of interest. Additionally, the ESS as a proportion of the sample size before matching was reasonably high (71.2–77.4%), suggesting a large overlap between the BE HEARD trial population and SUNRISE/SUNSHINE trial population.

There were some differences between the bimekizumab and secukinumab trials for certain baseline characteristics (Table 11). For example, patients in the bimekizumab trials had higher mean AN counts (range: 16.0, 17.7) compared to the secukinumab trials (range: 12.8, 13.3) and higher mean DT counts (range: 3.4, 5.1) compared to the secukinumab trials (range: 2.6, 2.7), which may indicate that the patients in the bimekizumab trials had more severe disease than those in the secukinumab trials [1, 2, 48, 115]. However, both the NMA and MAIC results generally favoured bimekizumab compared to secukinumab, even after differences in baseline characteristics had been adjusted for in the MAIC analysis.

The week 48–52 analysis is subject to the general limitations applying to unanchored MAICs: the analysis could not be placebo-adjusted and relies on the assumption of no unmeasured confounding variables.

B.2.9.6 Summary of NMA and MAIC findings

At week 16, bimekizumab Q2W could be compared with secukinumab Q2W and Q4W by means of an NMA. The results showed that for HiSCR50, HiSCR75, HiSCR90 and HiSCR100, patients treated with bimekizumab 320 mg Q2W were statistically significantly more likely to achieve a treatment response than those receiving secukinumab 300 mg Q2W and Q4W.

Improvements in IHS4, an outcome which is important to patients due to the inclusion of DTs, were also statistically significantly greater with bimekizumab 320 mg Q2W than with secukinumab 300 mg Q2W and Q4W, while patients were also significantly more likely to achieve an IHS4-55 response with bimekizumab 320 mg Q2W.

NMA results for week 16 change from baseline in DT count numerically favoured bimekizumab Q2W over secukinumab 300 mg Q2W and statistically significantly favoured

bimekizumab Q2W over secukinumab 300 mg Q4W, with bimekizumab having the highest probability of being the most effective therapy.

NMA results for week 16 change from baseline in AN count and for skin pain responses, numerically favoured bimekizumab Q2W over secukinumab 300 mg Q2W and Q4W, with bimekizumab having the highest probability of being the most effective therapy for both outcomes.

In the analysis of HiSCR50 among the subgroup of patients with prior biologic experience, bimekizumab 320 mg Q2W had the highest probability of being the most effective treatment. In the AN count analysis among the biologic-experienced subgroup, numerically larger mean percentage reductions were seen in the bimekizumab 320 mg Q2W group than the secukinumab 300 mg Q2W and Q4W groups.

Week 48–52 data for HiSCR50, HiSCR75 and HiSCR90 informed an unanchored MAIC to compare bimekizumab and secukinumab. The results for bimekizumab 320 mg Q2W/Q4W versus secukinumab 300 mg Q2W and versus Q4W were highly consistent across outcomes, with bimekizumab 320 mg Q2W/Q4W strongly favoured over both secukinumab doses.

Together, these results show that treatment with bimekizumab 320 mg Q2W is consistently more likely to lead to clinical responses after the initial treatment period than secukinumab 300 mg Q2W and Q4W. Further, bimekizumab 320 mg Q2W/Q4W is statistically significantly more likely to be associated with maintenance of treatment responses up to 48 week than either secukinumab 300 mg Q4W, which is the recommended maintenance dose, or secukinumab 300 mg Q2W, which may be used for some patients, based on clinical response [103].

B.2.10 Adverse reactions

B.2.10.1 Summary of safety data for bimekizumab in hidradenitis suppurativa

Safety data in this submission are taken from the BE HEARD I and BE HEARD II phase 3 trials and analysed using the SS, which included all study participants who received at least one dose (full or partial) of investigational product, or the AMS, defined as all study participants who had received at least one dose (full or partial) of bimekizumab (see section B.2.4.1 for analysis set definitions).

Safety results for the individual trial populations are summarised in this section, with additional detailed data shown in Appendix F, Table 129 and Table 130. A detailed description of safety outcomes is presented in this section using the pooled BE HEARD trial population.

B.2.10.2 Safety results in BE HEARD I and BE HEARD II

TEAEs during the placebo-controlled initial treatment period in the BE HEARD trials are summarised in Table 46. An overview of TEAEs in the pooled patient population, including exposure-adjusted incidence rates (EAIRs) is presented in Table 47 and Table 48. The most common TEAEs and TEAEs of interest are shown in Table 49.

B.2.10.2.1 Exposure

In the initial treatment phase, 576 patients were treated with bimekizumab 320 mg Q2W, 285 with bimekizumab 320 mg Q4W and 146 with placebo, corresponding to 175, 87 and 45 patient-years of exposure (PYE), respectively [137]. Over the entire trial period, there were 809 PYE to bimekizumab [137].

B.2.10.2.2 Summary of adverse events

TEAEs are summarised in Table 46, Table 47 and Table 48. During the initial treatment period, the incidence and exposure-adjusted incidence rate were similar across the bimekizumab and placebo groups. Serious TEAEs were infrequent but were reported at a higher incidence and rate for patients treated with bimekizumab than for those receiving placebo [115, 129].

B.2.10.2.3 Treatment-emergent adverse events leading to discontinuation

Few patients discontinued treatment as a result of TEAEs, but discontinuation due to TEAEs was more common in the bimekizumab groups than in the placebo group (Table 47) [129].

B.2.10.2.4 Common treatment-emergent adverse events

The most commonly reported TEAEs were hidradenitis, coronavirus infection, oral candidiasis, diarrhoea and headache (Table 49). Hidradenitis occurred at a higher rate in the placebo group than in the bimekizumab arms, while oral candidiasis was more frequent among patients treated with bimekizumab 320 mg Q2W than in the other groups. Most oral candidiasis cases were mild to moderate and did not lead to discontinuation [137].

Table 46 Overview of safety outcomes to week 16 in BE HEARD I and BE HEARD II (SS)

Safety outcome, n (%)	BE HEARD I			BE HEARD II		
	BKZ 320 mg Q2W (n = 286)	BKZ 320 mg Q4W (n = 143)	Placebo (n = 72)	BKZ 320 mg Q2W (n = 290)	BKZ 320 mg Q4W (n = 142)	Placebo (n = 74)
Any TEAE	192 (67.1%)	94 (65.7%)	48 (66.7%)	187 (64.5%)	73 (51.4%)	42 (56.8%)
Serious TEAEs	6 (2.1%)	4 (2.8%)	0	9 (3.1%)	3 (2.1%)	0
TEAEs leading to discontinuation	10 (3.5%)	6 (4.2%)	1 (1.4%)	12 (4.1%)	3 (2.1%)	0

Q2W, every 2 weeks; Q4W, every 4 weeks; SS, safety set; TEAE, treatment-emergent adverse event.
Source: Kimball *et al.* 2023, AAD presentation [115].

Table 47 Overview of safety outcomes to week 16 in pooled BE HEARD I and BE HEARD II population (SS)

Safety outcome	BKZ 320 mg Q2W (n = 576)		BKZ 320 mg Q4W (n = 285)		PBO (n = 146)	
	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)
Any TEAE	379 (65.8%)	398.2 (359.1–440.4)	167 (58.6%)	333.5 (284.8–388.1)	90 (61.6%)	348.6 (280.3–428.5)
Serious TEAEs	15 (2.6%)	8.6 (4.8–14.3)	7 (2.5%)	8.1 (3.3–16.8)	0	0
Severe TEAEs	20 (3.5%)	11.6 (7.1–17.9)	8 (2.8%)	9.3 (4.0–18.4)	2 (1.4%)	4.5 (0.5–16.3)
TEAEs leading to discontinuation	22 (3.8%)	12.8 (8.0–19.4)	9 (3.2%)	10.5 (4.8–19.9)	1 (0.7%)	2.3 (0.1–12.6)

BKZ, bimekizumab; EAIR, exposure-adjusted incidence rate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SS, safety set; TEAE, treatment-emergent adverse event. Source: Zouboulis *et al.* 2023a, EADV presentation [129].

Table 48 Overview of safety outcomes to week 48 in pooled BE HEARD I and BE HEARD II population (AMS)

Safety outcome	BKZ 320 mg Q2W/Q2W (n = 285)		BKZ 320 mg Q2W/Q4W (n = 291)		BKZ 320 mg Q4W/Q4W (n = 285)		BKZ 320 mg total (n = 995)	
	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)
Any TEAE	248 (87.0%)	297.3 (261.4–336.7)	252 (86.6%)	326.4 (287.4–369.3)	235 (82.5%)	255.2 (223.6–290.0)	837 (84.1%)	287.0 (267.9–307.1)
Serious TEAEs	23 (8.1%)	9.9 (6.3–14.8)	13 (4.5%)	5.4 (2.8–9.2)	20 (7.0%)	8.6 (5.3–13.3)	64 (6.4%)	8.1 (6.3–10.4)
Severe TEAEs	30 (10.5%)	13.1 (8.9–18.7)	15 (5.2%)	6.2 (3.5–10.2)	25 (8.8%)	10.8 (7.0–16.0)	81 (8.1%)	10.4 (8.2–12.9)
TEAEs leading to discontinuation	17 (6.0%)	7.2 (4.2–11.5)	20 (6.9%)	8.3 (5.1–12.8)	21 (7.4%)	9.0 (5.6–13.7)	67 (6.7%)	8.5 (6.6–10.8)

AMS, active medication set; BKZ, bimekizumab; EAIR, exposure-adjusted incidence rate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event. Source: Zouboulis *et al.* 2023a, EADV presentation [129].

Table 49 Common TEAEs and TEAEs of interest in pooled BE HEARD I and BE HEARD II population (SS, AMS)

Safety outcome	Initial treatment period (weeks 0–16)						Initial and maintenance treatment period (weeks 0–48)	
	BKZ 320 mg Q2W (n = 576) [PY = 175]		BKZ 320 mg Q4W (n = 285) [PY = 87]		PBO (n = 146) [PY = 45]		BKZ 320 mg total [a] (n = 995) [PY = 809]	
	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)
Most common TEAEs [b]								
Hidradenitis	44 (7.6%)	26.1 (19.0–35.1)	25 (8.8%)	30.2 (19.5–44.5)	15 (10.3%)	35.3 (19.8–58.2)	186 (18.7%)	25.7 (22.1–29.6)
Coronavirus infection	20 (3.5%)	11.6 (7.1–17.9)	5 (1.8%)	5.8 (1.9–13.5)	2 (1.4%)	4.5 (0.5–16.2)	107 (10.8%)	14.0 (11.4–16.9)
Oral candidiasis	41 (7.1%)	24.2 (17.4–32.8)	7 (2.5%)	8.2 (3.3–16.8)	0	0	111 (11.2%)	14.7 (12.1–17.7)
Diarrhoea	36 (6.3%)	21.3 (15.0–29.6)	17 (6.0%)	20.5 (11.9–32.8)	7 (4.8%)	16.3 (6.5–33.5)	85 (8.5%)	11.2 (8.9–13.8)
Headache	40 (6.9%)	23.9 (17.1–32.5)	15 (5.3%)	18.0 (10.1–29.6)	10 (6.8%)	23.4 (11.2–43.0)	86 (8.6%)	11.3 (9.1–14.0)
TEAEs of interest								
Infections and infestations	193 (33.5%)	134.9 (116.6–155.4)	91 (31.9%)	126.8 (102.1–155.7)	30 (20.5%)	76.4 (51.5–109.0)	578 (58.1%)	115.5 (106.2–125.3)
Serious infections	1 (0.2%)	0.6 (0.0–3.2)	0	0	0	0	16 (1.6%)	2.0 (1.1–3.2)
Opportunistic infections [c]	1 (0.2%)	0.6 (0.0–3.2)	2 (0.7%)	2.3 (0.3–8.3)	0	0	12 (1.2%)	1.5 (0.8–2.6)
Fungal infections	75 (13.0%)	45.6 (35.8–57.1)	35 (12.3%)	42.6 (29.7–59.2)	1 (0.7%)	2.3 (0.1–12.6)	236 (23.7%)	34.2 (30.0–38.9)
Candida infections	48 (8.3%)	28.5 (21.0–37.8)	22 (7.7%)	26.3 (16.5–39.8)	0	0	153 (15.4%)	20.9 (17.7–24.5)
Oral candidiasis [d]	41 (7.1%)	24.2 (17.4–32.8)	7 (2.5%)	8.2 (3.3–16.8)	0	0	111 (11.2%)	14.7 (12.1–17.7)
Neutropenia	0	0	0	0	0	0	1 (0.1%)	0.1 (0.0–0.7)
Hypersensitivity reaction [e]	64 (11.1%)	38.6 (29.7–49.3)	23 (8.1%)	27.6 (17.5–41.5)	5 (3.4%)	11.5 (3.7–26.9)	189 (19.0%)	26.6 (22.9–30.6)
Dermatitis and eczema	35 (6.1%)	20.6 (14.4–28.7)	15 (5.3%)	17.8 (10.0–29.3)	4 (2.7%)	9.2 (2.5–23.4)	122 (12.3%)	16.3 (13.6–19.5)
Serious hypersensitivity reaction	0	0	0	0	0	0	1 (0.1%)	0.1 (0.0–0.7)
Adjudicated suicidal ideation/behaviour	1 (0.2%)	0.6 (0.0–3.2)	1 (0.4%)	1.2 (0.0–6.4)	0	0	5 (0.5%)	0.6 (0.2–1.4)

Safety outcome	Initial treatment period (weeks 0–16)						Initial and maintenance treatment period (weeks 0–48)	
	BKZ 320 mg Q2W (n = 576) [PY = 175]		BKZ 320 mg Q4W (n = 285) [PY = 87]		PBO (n = 146) [PY = 45]		BKZ 320 mg total [a] (n = 995) [PY = 809]	
	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)
Adjudicated MACE	0	0	0	0	0	0	3 (0.3%)	0.4 (0.1–1.1)
Hepatic events	14 (2.4%)	8.1 (4.4–13.6)	5 (1.8%)	5.8 (1.9–13.5)	4 (2.7%)	9.2 (2.5–23.6)	44 (4.4%)	5.6 (4.1–7.5)
> 5x ULN elevation of AST/ALT	3 [f] (0.5%)	1.7 [f] (0.4–5.0)	0 [g]	0 [g]	0 [h]	0 [h]	8 [i] (0.8%)	1.0 [i] (0.4–2.0)
Malignancies [j]	1 (0.2%)	0.6 (0.0–3.2)	0	0	0	0	4 (0.4%)	0.5 (0.1–1.3)
Definite or probable adjudicated IBD	1 (0.2%)	0.6 (0.0–3.2)	3 (1.1%)	3.5 (0.7–10.2)	0	0	7 (0.7%) [k]	0.9 (0.3–1.8)

TEAEs were coded using MedDRA v19.0 and reported as raw incidence (percentages) and EAIRs. EAIRs were defined as incidence of new cases per 100 PY, with 95% CIs. Data and any adjudication are shown as of the data cut-off (15 November 2022).

[a] Data were pooled for all patients who received ≥ 1 BKZ 320 mg dose to week 48 (BKZ Total), including patients who switched at week 16 from PBO to BKZ 320 mg Q2W (n=134; for these patients, events are reported after the switch to BKZ and for 32 weeks of BKZ treatment).

[b] Top three most common TEAEs are presented for the initial (Weeks 0–16: hidradenitis, headache, diarrhoea) treatment period, and for BKZ treatment groups in the combined initial and maintenance (Weeks 0–48: hidradenitis, oral candidiasis, coronavirus infection) treatment periods.

[c] Opportunistic infections were localised (non-systemic) events, as defined by sponsor-defined search criteria and medical review.

[d] Incidence of oral candidiasis was highest among patients who had received BKZ Q2W in the initial treatment period.

[e] Events were mostly driven by events related to dermatitis and eczema; there were no incidences of anaphylactic reactions related to BKZ.

[f] n=144.

[g] n=282.

[h] n=572.

[i] n=988.

[j] Includes malignant tumours (excluding unspecified).

[k] 4 cases led to discontinuation.

ALT, alanine aminotransferase; AMS, active medication set; AST, aspartate aminotransferase; BKZ, bimekizumab; CI, confidence interval; EAIR, exposure-adjusted incidence rate; IBD, inflammatory bowel disease; MACE, major adverse cardiac event; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PY, patient-years; Q2W, every 2 weeks; Q4W, every 4 weeks; SS, safety set; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Source: Bechara *et al.* 2023, EADV presentation [137].

B.2.10.2.5 Serious treatment-emergent adverse events

In both BE HEARD trials, the incidence of serious TEAEs was low in the initial treatment period (BE HEARD I, 2.3% of bimekizumab-treated patients; BE HEARD II, 2.8% of bimekizumab-treated patients), with a similar incidence in the bimekizumab 320 mg Q2W and Q4W groups (Table 46) [2].

Over the entire 48-week treatment period, serious TEAEs were experienced by 6.4% of patients treated with bimekizumab (Table 48). In BE HEARD I, serious TEAEs, by preferred term, reported for more than one patient were hidradenitis (7 patients), suicidal ideation (4 patients), cellulitis (2 patients), and nephrolithiasis (2 patients) [1]. In BE HEARD II, serious TEAEs, by preferred term, reported for more than one patient were hidradenitis (4 patients) and skin pain (2 patients) [2].

In both trials the majority of serious TEAEs were assessed as not related to bimekizumab by the study investigators and did not lead to study discontinuation [2].

B.2.10.2.6 Treatment-emergent adverse events of interest

TEAEs during the initial treatment period are shown in Table 49. TEAEs of interest to week 48 are shown in Table 49 for the overall population.

During the 48-week study period, serious infections occurred in 16 patients (1.6%). A total of 153 patients (15.4%) experienced *Candida* infections, of whom 111 (11.2%) had oral candidiasis. Hypersensitivity reactions were reported in 189 (19.0%) patients; the majority of these were dermatitis or eczema. Most oral candidiasis cases and hypersensitivity reactions were mild to moderate and did not lead to discontinuation [137].

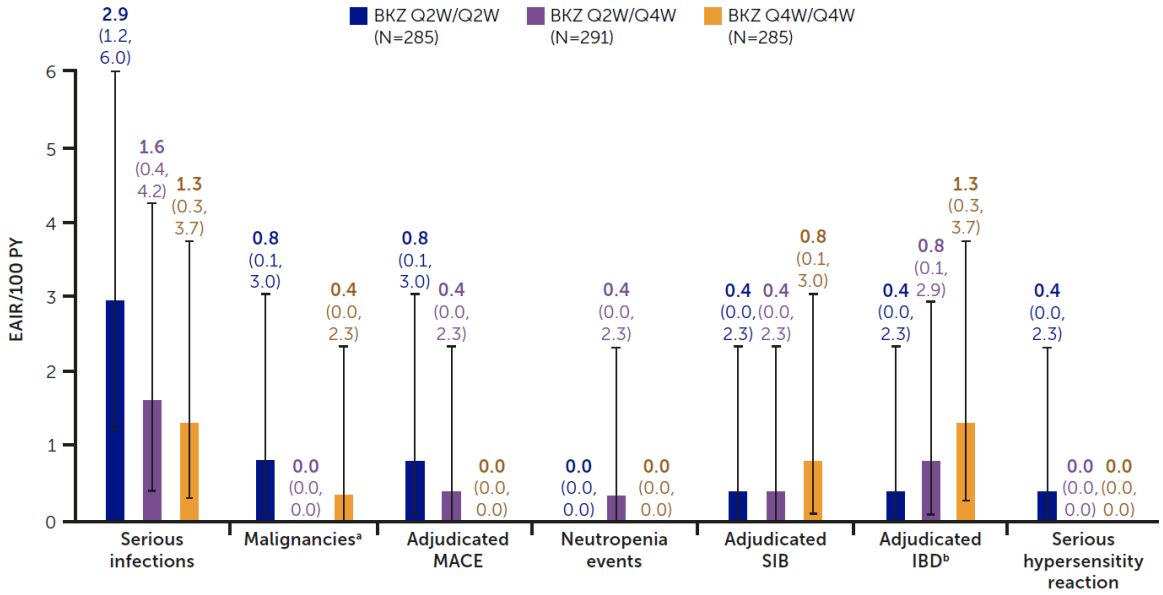
Hepatic events were reported in 44 patients (4.4%). No cases were associated with sequelae and the majority of patients were asymptomatic. Transient alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevations > 5 x the upper limit of normal occurred in eight patients (0.8%); the majority of cases were mild or moderate and most had an explanation or confounding factors [137].

Adjudicated definite or probable inflammatory bowel disease (IBD) occurred in seven patients (0.7%); four led to discontinuation. No new IBD events occurred in the eight patients with history of IBD [137].

Incidences of neutropenia, malignancies and adjudicated major adverse cardiac events (MACE) were low [137]. Incidence of adjudicated suicidal ideation and behaviour was in line with expectation for the study population, with no events of completed suicide [137].

TEAEs of interest to week 48 are shown in Figure 28 according to treatment regimen [137]. Serious infections were more frequent among patients treated with bimekizumab 320 mg Q2W maintenance therapy than among those receiving bimekizumab 320 mg Q4W, although confidence intervals for exposure-adjusted incidence rate estimates were wide and overlapping. The incidence of other TEAEs of interest was low and similar across bimekizumab regimens (Table 49) [137].

Figure 28 TEAEs of interest to week 48 by treatment regimen (AMS)



TEAEs were coded using MedDRA v19.0 and reported as EAIRs defined as incidence of new cases per 100 PY, with 95% CIs.

Data and any adjudication are shown as of the data cut-off (15 November 2022).

Error bars represent 95% CIs.

[a] Includes malignant tumours (excluding unspecified).

[b] Includes any TEAE adjudicated as definite or probable IBD.

BKZ, bimekizumab; CI, confidence interval; EAIR, exposure-adjusted incidence rate; IBD, inflammatory bowel disease; MACE, major adverse cardiac event; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient-years; Q2W, every 2 weeks; Q4W, every 4 weeks; SIB, suicidal ideation and behaviour; TEAE, treatment-emergent adverse event.

Source: Bechara *et al.* 2023, EADV presentation [137].

B.2.10.2.7 Deaths

Across the programme, one patient with significant cardiovascular history died of congestive heart failure, which was considered unrelated to bimekizumab treatment by the study investigator (BE HEARD I: bimekizumab 320 mg Q2W/Q2W group) [137].

B.2.10.3 Summary of safety data in BE HEARD EXT

Preliminary data for an additional year of treatment with bimekizumab in the BE HEARD EXT open-label extension study are summarised in Table 50 [128]. No new safety issues were identified.

Table 50 Overview of safety outcomes during BE HEARD EXT (OLE set)

Safety outcome, n (%)	Bimekizumab 320 mg Q2W (n = 604)	Bimekizumab 320 mg Q4W (n = 507)	Bimekizumab 320 mg total (n = 657)
Any TEAE	[redacted]	[redacted]	[redacted]
Serious TEAEs	[redacted]	[redacted]	[redacted]
Severe TEAEs	[redacted]	[redacted]	[redacted]
TEAEs leading to discontinuation	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]

CI, confidence interval; OLE, open-label extension; TEAE, treatment-emergent adverse event.
Source: BE HEARD EXT data tables [128].

B.2.10.4 Summary of safety data in bimekizumab phase 2 trial

Safety results in the bimekizumab phase 2 trial are summarised in Table 51. TEAE rates were similar in the bimekizumab, placebo and adalimumab arms and were mostly mild or moderate in intensity [116]. The incidence of serious TEAEs was low and similar across treatment arms, and none were considered related or led to discontinuation [116]. Four non-serious oral candidiasis events were observed in three patients in the bimekizumab group, all localised, mild or moderate infections and resolved with appropriate antifungal therapy [116].

Table 51 Summary of safety outcomes in bimekizumab phase 2 trial

Safety outcome, n (%) [events]	Bimekizumab (n = 46)	Placebo (n = 21)	Adalimumab (n = 21)
Any TEAE	32 (70%) [150]	13 (62%) [30]	15 (71%) [60]
Serious TEAEs	2 (4%) [2]	2 (10%) [4]	1 (5%) [2]
Anaemia	1 (2%) [1]	0	0
Myocardial infarction	0	1 (5%) [1]	0
Empyema	1 (2%) [1]	0	0
Headache	0	1 (5%) [1]	0
Dizziness	0	1 (5%) [1]	0
Hypoesthesia	0	1 (5%) [1]	0
Hidradenitis	0	0	1 (5%) [2]
TEAEs leading to discontinuation	1 (2%) [1]	0	0
Drug-related TEAEs	18 (39%) [48]	3 (14%) [4]	9 (43%) [29]
Severe TEAEs	3 (7%) [6]	1 (5%) [2]	2 (10%) [2]

TEAE, treatment-emergent adverse event.
Source: Glatt *et al.* 2021 [116].

B.2.10.5 Summary of safety data in real-world cohort

In the French real-world cohort described in section B.2.6.10.3, 21 of 72 patients (30%) reported an AE during the average follow-up period of 9 months. There were no severe AEs or AEs leading to discontinuation. The most common AE was oral candidiasis [140].

B.2.10.6 Summary of bimekizumab safety profile in other indications

Safety results from the BE HEARD trial programme are supported by additional data in other indications, all of which demonstrate a generally similar safety profile.

Three years of safety data for bimekizumab are available from three phase 3 plaque psoriasis trials (BE VIVID, BE READY, BE SURE) and their ongoing open-label extension (BE BRIGHT) [150]. Among 1495 patients with a total bimekizumab exposure of 3 876 patient-years, the most common TEAEs were nasopharyngitis, oral candidiasis, and upper respiratory tract infection (EAIRs of 15.0/100 PY, 10.1/100 PY, and 6.5/100 PY, respectively); 99.3% of oral candidiasis events were mild or moderate in severity, none were serious, and few led to discontinuation [150]. The rate of suicidal ideation and behaviour was low [150].

The safety of bimekizumab for psoriatic arthritis has been studied for up to 52 weeks in BE OPTIMAL, BE COMPLETE and the ongoing BE VITAL open-label extension, with no new safety signals identified [151, 152]. An increased incidence of oral candidiasis was seen with bimekizumab, with all events mild or moderate in severity [151, 152]. In addition, an open-label extension to a bimekizumab phase 2a trial in psoriatic arthritis found a consistent safety profile for up to three years [153].

Bimekizumab has also been investigated for 52 weeks in the BE MOBILE I and BE MOBILE II axial spondyloarthritis trials, with a safety profile similar to that seen in other indications [154]. A recent NMA of safety in axial spondyloarthritis trials found bimekizumab to have a safety profile comparable to that of other biologic/targeted synthetic disease-modifying anti-rheumatic drugs [155].

B.2.10.7 Overview of safety in relation to the decision problem

In total, the safety analyses in the bimekizumab HS phase 3 trials includes 809 PYE. The rate of TEAEs was similar in the bimekizumab and placebo groups; serious TEAEs were infrequent. In line with the bimekizumab mechanism of action, an increased incidence of oral candidiasis was seen with bimekizumab, compared with placebo, in the BE HEARD studies. Most oral candidiasis cases were mild to moderate and did not lead to discontinuation.

The safety results in the BE HEARD trials were consistent with the findings of bimekizumab trials in plaque psoriasis, psoriatic arthritis and axial spondyloarthritis. Overall, the results of the safety analyses show that bimekizumab is generally well tolerated.

B.2.11 Interpretation of clinical effectiveness and safety evidence

B.2.11.1 Principal findings of the BE HEARD clinical studies

The efficacy of bimekizumab 320 mg Q2W/Q4W for the treatment of moderate to severe HS in adults was demonstrated in the phase 3 BE HEARD I and BE HEARD II trials, both of which met their primary endpoints. The phase 3 trial results were consistent with the results of the earlier phase 2 study.

Clinical responses – HiSCR50, HiSCR75, HiSCR90 and HiSCR100

In the BE HEARD trials, initial treatment with bimekizumab 320 mg Q2W was superior to placebo in inducing HiSCR responses, with the majority of bimekizumab 320 mg Q2W-treated patients achieving HiSCR50 at week 16, and approximately 40% achieving HiSCR75 (see section B.2.6.3 and section B.2.6.4.1).

The effect of bimekizumab was both rapid and sustained during maintenance treatment with bimekizumab 320 mg Q4W. For 40.1% of patients treated with bimekizumab 320 mg Q2W/Q4W, a HiSCR50 response was seen after only 4 weeks. In addition, most patients retained their week 16 HiSCR responses during 32 weeks of subsequent bimekizumab 320 mg Q4W treatment, including 88.5% maintenance of HiSCR50 responses and 88.3% maintenance of HiSCR75 responses (see section B.2.6.5.2). By week 48, 33.0% of patients treated with bimekizumab 320 mg Q2W/Q4W had a HiSCR90 response, and 23.3% had achieved HiSCR100, indicating complete clearance of abscesses and inflammatory nodules (see section B.2.6.5).

Reductions in DTs

A limitation of HiSCR50 and the related measures is the lack of dynamic measurement of DTs, which can cause significant pain and impair patients' HRQoL (see section B.1.3.1). Patients treated with bimekizumab 320 mg Q2W/Q4W had larger mean reductions in DT count at week 16 than those receiving placebo, and 44.3% achieved zero DTs at week 48 (see section B.2.6.6.2). In addition, 61.0% of patients treated with bimekizumab 320 mg Q2W/Q4W who had ≥ 5 DTs at baseline achieved a reduction of at least 3 DTs at week 16; this increased to 66.2% at week 48.

Reductions in IHS4 disease severity

The IHS4 may provide a broader measure of clinical efficacy than HiSCR responses, because all lesion types are included in the calculated score (see section B.1.3.1.2), and is considered by clinicians to have greater relevance to clinical practice [16, 17, 65]. Treatment with bimekizumab 320 mg Q2W/Q4W was associated with substantial reductions in IHS4 disease severity: whereas 88.4% of patients had severe disease at baseline, only 47.3% had severe disease at week 16 and only 36.4% had severe disease at week 48. In addition, patients treated with bimekizumab 320 mg Q2W were more likely to have IHS4-55 responses at week 16 than those receiving placebo (see section B.2.6.7).

Improvements in skin pain

During the initial treatment period, bimekizumab 320 mg Q2W therapy led to statistically significant improvements in skin pain, with 36.7% of patients having a clinically meaningful improvement in pain in each of the BE HEARD trials, compared with 16.1% and 11.1% in the two placebo groups (mNRI for HS-ABX analysis; see section B.2.6.9.1).

Patients treated with bimekizumab 320 mg Q2W were more likely to have NRS30 skin pain responses at week 16 than those receiving placebo (49.9% vs 26.9%; mNRI for HS-ABX analysis; see section B.2.6.9.1). Patients in the bimekizumab 320 mg Q2W groups were more likely than those in the placebo group to have an HSSQ score of 0 (indicating no skin pain; 10.8% and 7.1% vs 2.3%; mNRI for HS-ABX analysis) at week 16; there was an

increase in the proportion of patients with HSSQ during maintenance treatment in all groups (see section B.2.6.9.1).

Improvements in HRQoL

Treatment with bimekizumab 320 mg Q2W/Q4W was also associated with statistically significant improvements in HRQoL (see section B.2.6.9). In total, 56.4% of patients with baseline DLQI ≥ 4 had a clinically meaningful improvement (≥ 4-point reduction in DLQI) after 16 weeks of treatment with bimekizumab 320 mg Q2W. In addition, larger mean improvements in all HiSQOL domains were seen at week 16 among patients treated with bimekizumab, compared with placebo; further improvements were observed by week 48.

Increases in efficacy after week 16

HiSCR50, HiSCR75, HiSCR90 and HiSCR100 responses among patients in the bimekizumab 320 mg Q2W/Q4W group continued to increase after week 16. In addition, continued improvements in AN count, DT count and IHS4 score were seen during the maintenance treatment period. Overall, the results observed during maintenance therapy in the BE HEARD trials are consistent with the maximum efficacy of bimekizumab 320 mg Q2W/Q4W being reached after week 16. This suggests that for patients without a HiSCR50 response at week 16 (for example, as modelled in section B.3 via the HiSCR25 partial response health state), continued treatment may further improve their symptoms and lead to a higher level of response.

Extension study results

As described in section B.1.3.3, it is common for patients treated with the currently available biological therapies for HS, adalimumab and secukinumab, to have an initial clinical response but lose this response by the end of 1 year of treatment [44-48]. Given the chronic nature of HS, there is therefore an unmet need for biologics with long-lasting efficacy.

For bimekizumab, long-term maintenance of treatment responses was investigated in the BE HEARD EXT extension study, which patients in the BE HEARD I and BE HEARD II trials were eligible to enter at the end of the parent studies.

[redacted]

Subgroup analysis results

To complement the results in the overall BE HEARD populations, subgroup analyses were conducted. These found bimekizumab 320 mg Q2W/Q4W to be consistently efficacious in inducing HiSCR50 responses regardless of patients' prior biologic use, disease severity, weight, sex and race (see section B.2.7). Subgroup analyses according to weight, sex and race are important because of the association between obesity and HS and the increased prevalence of HS seen in women compared with men and in people with an African–Caribbean background, compared with other groups.

Bimekizumab safety profile

As described in section B.2.10, treatment with bimekizumab 320 mg Q2W/Q4W was well tolerated by patients in BE HEARD I and II. The safety data observed in both trials were generally consistent with the known safety profile of bimekizumab, and no new safety signals were identified. No new safety issues were identified in the BE HEARD EXT open-label extension study.

Comparative efficacy

The efficacy of bimekizumab 320 mg Q2W at 16 weeks was compared with adalimumab 40 mg QW and secukinumab 300 mg Q2W and Q4W using an NMA (see section B.2.9; adalimumab results reported in Appendix D.1.5.6). The results showed that patients treated with bimekizumab 320 mg Q2W were statistically significantly more likely to achieve HiSCR50, HiSCR75, HiSCR90, HiSCR100 and IHS4-55 responses at week 16 than those receiving secukinumab 300 mg Q2W or Q4W. Bimekizumab 320 mg Q2W was associated with a statistically significantly greater mean reduction in DT count than secukinumab 300 mg Q4W, and had an 80.1% probability of being the most effective treatment (compared with 3.1% for secukinumab 300 mg Q2W). The results also suggest that bimekizumab 320 mg Q2W is likely to be more efficacious than secukinumab 300 mg Q2W and Q4W in reducing AN count and inducing NRS30 skin pain responses.

Across all outcomes assessed in an NMA for both the overall population and biologic-experienced subgroup, bimekizumab 320 mg Q2W consistently ranked first, measured as the proportion of simulations in which it was the most effective treatment (summarised in Table 52).

At week 48–52, bimekizumab 320 mg Q2W/Q4W was compared with secukinumab 300 mg Q4W using an unanchored MAIC (see section B.2.9.4). The results showed that patients treated with bimekizumab 320 mg Q2W/Q4W had significantly higher odds of patients achieving HiSCR50, HiSCR75 and HiSCR90 after maintenance therapy, compared with secukinumab 300 mg Q4W. In clinical practice, patients treated with secukinumab 300 mg Q4W may have their treatment up-titrated to Q2W, depending on clinical response [103]. The MAIC results showed that bimekizumab 320 mg Q2W/Q4W is also statistically significantly more efficacious in inducing week 48–52 HiSCR50, HiSCR75 and HiSCR90 responses than the secukinumab 300 mg Q2W regimen.

Table 52 Summary of week 16 NMA outcomes

Outcome	Proportion of simulations in which treatment is most efficacious			
	Bimekizumab 320 mg Q2W	Bimekizumab 320 mg Q4W	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W
Overall population				
HiSCR50	**57.1%**	36.2%	0.3%	0.3%
HiSCR75	**94.4%**	4.3%	0.1%	0.3%
HiSCR90	**64.3%**	35.1%	0.0%	0.2%
HiSCR100	**40.8%**	35.6%	0.4%	0.3%
IHS4-55	**45.7%**	27.4%	0.0%	0.0%
IHS4 CfB	**83.2%**	15.1%	1.7%	0.0%
% AN count CfB	**49.7%**	3.1%	4.7%	5.1%
DT count CFB	**80.1%**	2.7%	3.1%	0.1%
NRS30	**82.5%**	6.8%	8.8%	1.8%
Biologic-experienced patients				
HiSCR50	**59.1%**	27.7%	6.0%	7.2%
% AN count CfB	**57.5%**	26.0%	8.1%	8.4%

The treatment with the highest percentage for each outcome is highlighted in **bold**. Percentages do not add up to 100% due to exclusion of adalimumab; see full tables in Appendix D.1.5.6.

Fixed effect models, with placebo adjustment for HiSCR50, HiSCR75, HiSCR90 and HiSCR100 in the overall population analysis. NRS30: ≥ 30% reduction and reduction of ≥ 2 units from baseline in Patient's Global Assessment of Skin Pain by "worst skin pain" on a continuous numerical rating scale, assessed in patients with a baseline numerical rating scale of ≥ 3.

AN, abscess and inflammatory nodule; BKZ, bimekizumab; CrI, credible interval; DT, draining tunnel; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; IHS4, International Hidradenitis Suppurativa Severity Score System; MI, multiple imputation; mNRI, modified non-responder imputation; NRS, numerical rating scale; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab.

B.2.11.2 Strengths and limitations of the evidence base

Strengths and limitations

A key strength of the BE HEARD trials is that they are the first studies to include HiSCR75 as a key ranked secondary endpoint. In both trials, HiSCR75 clinical response rates at week 16 were statistically significantly higher among patients treated with bimekizumab 320 mg Q2W than among those receiving placebo (section B.2.6.4.1; see also Appendix D.5, Table 116 and Table 118 for results using the prespecified intercurrent event definition) [115]. The deeper level of response measured with the HiSCR75 threshold, representing more complete resolution of symptoms than HiSCR50, is an important goal for patients with HS [60], and is beginning to be used as a primary endpoint in HS clinical trials (see section B.1.3.1.2) [64].

A further strength of the BE HEARD evidence is the inclusion of long-term data from BE HEARD EXT, which provided evidence of a durable response in patients taking bimekizumab for up to 96 weeks (see section B.2.6.10.1). This study showed that, in the overall BE HEARD EXT population, HiSCR responses were generally maintained or improved during the second year of treatment with bimekizumab. IHS4-55 responses and proportion of patients in the IHS4 mild category were also similar at weeks 48 and 96 in the overall BE HEARD EXT population.

The prespecified definition of intercurrent events in the BE HEARD trials is strict with regard to systemic antibiotic use: participants who received a systemic antibiotic for any reason (all-ABX) during the study period were deemed to have experienced an intercurrent event. This approach, which was required for regulatory purposes, is particularly conservative for binary endpoints (such as HiSCR50 response). Whereas continuous data are set to missing and subject to imputation, binary endpoints are subject to a cumulative impact – deemed non-responder status remains until the end of the study, so as more participants experience intercurrent events, the rate of non-response accumulates.

Consequently, a limitation of the BE HEARD trials is that the prespecified intercurrent event definition limits the comparability of the trial data with other studies, as discussed in sections B.2.2 and B.2.4.2. Instead, a *post hoc* analysis was employed in which systemic antibiotic use was defined as an intercurrent event only if prescribed for HS. This approach accounts for the high level of systemic antibiotic use in the BE HEARD trials (the majority of which was not rescue medication for HS; see section B.2.4.6), which is reflective of clinical practice, and allows for a comparison with the secukinumab SUNSHINE and SUNRISE trials (a detailed comparison of the BE HEARD trials with the phase 3 studies of secukinumab is presented in Appendix D.1.4.5). This analysis is consistent with advice received from UK clinicians at an HS advisory board, who agreed that this would be the most appropriate approach.

Relevance to UK clinical practice

The results of the BE HEARD trial are expected to be applicable to UK clinical practice. The enrolled population matches the anticipated indication: adult patients with moderate to severe HS. As might be expected in clinical practice, a proportion of patients had received previous biological therapy (24.8% in BE HEARD I and 13.0% in BE HEARD II; most prior biologic use was adalimumab; see section B.2.3.3). A subgroup analysis according to prior biologic use provides specific evidence for these patients, with consistent efficacy demonstrated for bimekizumab 320 mg Q2W/Q4W across groups (see section B.2.7) [133]. Subgroup analysis results also showed bimekizumab 320 mg Q2W/Q4W to be efficacious for patients using systemic antibiotics at baseline. In general, the consistent results seen across subgroups shows that bimekizumab is likely to broadly efficacious across the HS population. In one analysis, bimekizumab was found to have efficacy in Black/African-American patients similar to that in the overall study population (see section B.2.7) [136]; this may also be relevant to UK practice given HS is more common among people with an African–Caribbean background. In addition, HiSCR50 response rates were similar for male and female patients (see section B.2.7) [135]. This finding is of particular importance because of the increased prevalence of HS seen in women compared with men. In addition, the similar efficacy seen in the BE HEARD trials contrasts with the results seen for some other biological therapies in other indications (for example, TNFi therapies in psoriatic arthritis and ankylosing spondylitis), in which higher treatment effectiveness has been observed in men, compared with women [156, 157].

As described above, the BE HEARD trial results were analysed according to a *post hoc* definition of intercurrent events, which allows for the use of systemic antibiotics for

indications other than HS. This is relevant to UK clinical practice, in which patients may receive treatment for multiple conditions. In addition, results are presented using an OC analysis, including data for patients receiving rescue antibiotics for HS. Again, this is relevant to the outcomes that might be observed in clinical practice, where concomitant antibiotic use is common (see section B.1.3.3).

Some patients treated with the currently available biological therapies for HS, adalimumab and secukinumab, have an initial clinical response but lose this response by the end of one year of treatment [44-48]. The 96-week BE HEARD EXT data, which provide evidence of a durable response when considering key HiSCR and IHS4 outcomes, show that bimekizumab may help address this need for biologic treatments with long-term efficacy.

B.2.11.3 Summary

Bimekizumab is the first treatment option for HS that targets IL-17F as well as IL-17A. Accordingly, bimekizumab inhibits IL-17A homodimers, IL-17F homodimers and IL-17A/F heterodimers, in contrast to other IL-17 biologics such as secukinumab that inhibit the biological function only of IL-17A homodimers and IL-17A/F heterodimers.

Overall, the results of the BE HEARD trials show that bimekizumab 320 mg Q2W/Q4W is an efficacious, well-tolerated treatment option for adult patients with moderate to severe HS, whether or not they have received prior treatment with a TNFi. Compared with placebo, bimekizumab 320 mg Q2W/Q4W treatment led to a higher rate of all levels of HiSCR responses up to and including HiSCR100, as well as substantial reductions in DT count and in disease severity, measured with the IHS4. These responses were maintained up to week 48 and led to substantial improvements in HRQoL, an outcome of key importance for patients. Additionally, evidence from the the BE HEARD EXT study showed that response levels were generally similar at 48 weeks and 96 weeks when considering key HiSCR and IHS4 outcomes.

The efficacy of bimekizumab 320 mg Q2W/Q4W and secukinumab 300 mg Q2W or Q4W was compared in an NMA and a MAIC assessing key clinical outcomes. The results showed that bimekizumab 320 mg Q2W/Q4W is a statistically significantly more efficacious therapy than either secukinumab regimen, both at week 16 (when considering HiSCR and IHS4 outcomes) and at week 48–52 after maintenance therapy (when considering HiSCR outcomes). For all NMA and MAIC analyses included in this submission, point estimates favoured bimekizumab 320 mg Q2W/Q4W over both secukinumab regimens.

Given the need for additional well-tolerated, efficacious and durable therapies for moderate to severe HS, bimekizumab 320 mg Q2W/Q4W represents a step-change in the treatment of patients in its proposed position: adults for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment.

B.3 Cost effectiveness

Summary

Model framework

- A *de novo* cost-utility model was developed to compare bimekizumab with secukinumab or with BSC for the treatment of patients with moderate to severe HS for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment.
- The model's perspective adheres to the NICE reference case.
- The mathematical framework is an extension of models presented at previous TAs. It incorporates key features such as treatment response from HiSCR50 to HiSCR90, stopping rules for non response and partial response, all-cause discontinuation, and patient mortality.

Model input

- The clinical trial evidence was used to reflect the baseline efficacy and safety of bimekizumab.
- In the absence of direct evidence, the comparative effectiveness of secukinumab and BSC in the economic model was based on an NMA conducted on the response levels at 16 weeks.
- The cost and utility of treating 20.8% of patients on BSC with adalimumab was included in the model. No additional costs or utility were assumed for patients receiving non-biologic therapies while on BSC, assuming that the use of concomitant medication for all comparators was reflected in the background therapy administered in the BE HEARD I and II.
- EQ-5D evidence collected in BE HEARD I and BE HEARD II was used to populate the model utility values associated with the level of response. For patients on active treatment (bimekizumab, secukinumab and a proportion of BSC on adalimumab), the analysis assumed the utility values observed in the bimekizumab arm. For a proportion of patients on BSC without active biologic treatment, the analysis assumed the observed placebo utility data from weeks 0–16.
- The synthesis of costs and resource use followed previous practice and TAs in HS, including, where relevant, biosimilar prices, surgery and other types of health care professionals.

Model results

- Bimekizumab is a cost-effective option for treating moderate-to-severe HS compared to secukinumab and BSC. It was found to be cost-effective at a willingness to pay threshold of £30,000 per QALY.
- Sensitivity analysis (probabilistic and deterministic) suggests that the model results are robust to input changes and uncertainty.

B.3.1 Published cost-effectiveness studies

Identification and selection of relevant cost-effectiveness studies is described in Appendix G. In brief, searches of relevant publication databases and grey literature sites were conducted on 6 November 2023. The SLR identified five published economic evaluations, all conducted from a UK perspective (Table 53) [42, 44, 158-160]. These described the NICE HTAs of adalimumab [42, 159] and secukinumab [44], the SMC evaluation of adalimumab [158], and

an early economic modelling study based on adalimumab [160]. These studies, all of which used a similar model structure, were used to inform the development of the bimekizumab economic model.

Table 53 Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
Willems [160]	2020	State transition Markov models consisting of five health states differentiated by HiSCR response rates, and using a lifetime modelling horizon	Adults with moderate to severe HS	Adalimumab: 13.596; Candidate drug: 14.073	Adalimumab: £209,465; Candidate drug: £272,993 [GBP, 2019]	£132,952
SMC 1143/16 [158]	2016			NR	NR	£22,519
NICE TA392 [42]; Tappenden [159]	2016; 2017			Deterministic: Adalimumab 12.58; Supportive care 11.63 Probabilistic: Adalimumab 12.61; Supportive care 11.64	Deterministic: Adalimumab £140,342; Supportive care £128,647 Probabilistic: Adalimumab £142,407; Supportive care £129,062 [GBP, 2013–14]	NICE determined the ICER to be between £28,500 and £33,200 per QALY gained or lower.
NICE TA935 [44]	2023			NR	NR	Deterministic: £18,439 Probabilistic: £18,099

Abbreviations: QALY, quality-adjusted life year. ICER, incremental cost-effectiveness ratio; SMC, Scottish Medicines Consortium ; HiSCR, hidradenitis suppurativa clinical response; HS, hidradenitis suppurativa; NICE, National Institute for health and Care Excellence; NR, not reported.

B.3.2 Economic analysis

The objective of the economic analysis was to evaluate the cost-effectiveness of bimekizumab as compared with secukinumab or with BSC for the treatment of patients with moderate to severe HS for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment (see section B.1.3.4).

The SLR of economic evaluations identified five studies [42, 44, 158-160], none of which included bimekizumab as a comparator. A *de novo* cost-utility analysis (CUA) was developed to evaluate bimekizumab against the above comparators.

The analysis included a state transition (Markov) model that borrowed from the mathematical framework and structure of the economic analyses considered under TA392 [42] and TA935 [44]. The structure of the model was extended to include HiSCR90 response. This extension of the cohort categorisation to include the higher response captures important elements of HS missing from previous analyses.

The NICE reference case was followed in all aspects of the CUA design and perspective; including costs reflecting the NHS and personal social services (PSS) and outcomes reflected as quality-adjusted life years (QALYs) gained.

B.3.2.1 Patient population

In alignment with the clinical evidence, in the base-case analysis the model cohort reflected the patient characteristics of the BE HEARD I and II trial populations, which consisted of patients aged at least 18 years who had a diagnosis of moderate to severe HS.

B.3.2.2 Model structure

The model structure is presented in Figure 29. The model consists of six states, as follows:

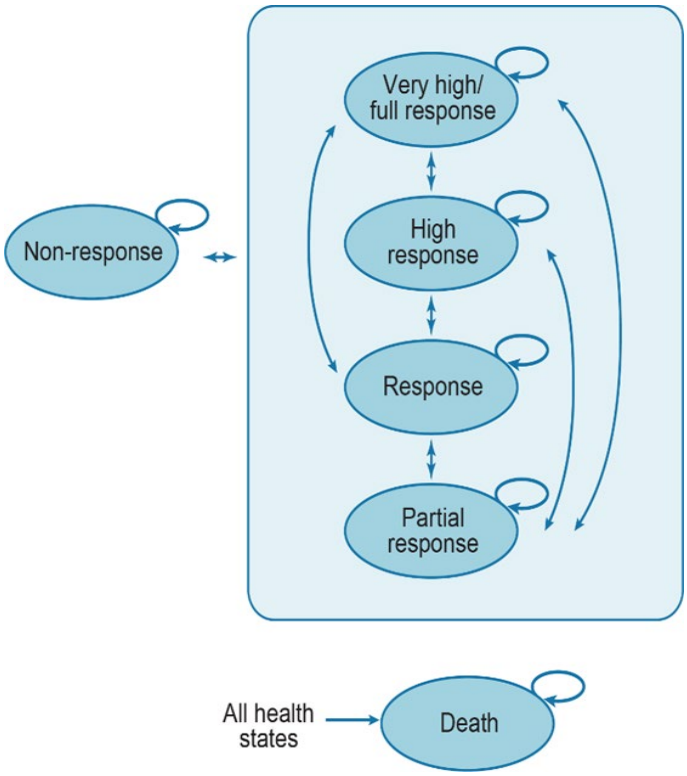
1. “Non-response” (HiSCR<25), corresponding to a less than 25% reduction in total AN count and/or an increase in abscesses or draining tunnels
2. “Partial response” (HiSCR25), a reduction in total AN count of 25% and less than 50% and no increase in abscesses or draining tunnels
3. “Response” (HiSCR50), a reduction of 50% and less than 75% and no increase in abscesses or draining tunnels
4. “High response” (HiSCR75), a reduction of 75% and less than 90% and no increase in abscesses or draining tunnels
5. “Very high response” (HiSCR90), showing an AN count reduction from baseline of 90-100% and no increase in abscesses or draining tunnels
6. “Death”, absorbing health state.

By extending and separating high response (HiSCR75+) to over HiSCR75 (high response) and HiSCR90 (very high response) the model reflects more accurately the clinical findings of BE HEARD I and II. Sensitivity analysis considering a model structure comparable with the model presented in TA935 [44], in which the “Very high response” health state was subsumed within the “High response” category.

Costs and health outcomes were evaluated over patients’ lifetime at time increments of 4 weeks (cycle length), corresponding to the dosing frequency seen in the BE HEARD I and II trials. Half-cycle correction was applied to the model outcomes. Future costs and health outcomes were discounted at an annual rate of 3.5%.

The cohort was assumed to start in the non-response health state. From this health state a proportion of the cohort could respond at a different level (25, 50, 75 or 90%). For the proportion of responders, transitions to states representing further improvement or deterioration (drop in response category) were possible, as was remaining in the same response category.

Figure 29 Base-case CUA model structure



Abbreviations: CUA, cost-utility analysis.

Note: Response was assessed based on HiSCR response thresholds. “Very high response” was defined as at least 90% total AN count reduction from baseline, with no increase in abscesses or draining tunnels. “High response” was defined as at least 75% but less than 90% total AN count reduction, with no increase in abscesses or draining tunnels. “Response” was defined as at least 50% but less than 75% total AN reduction from baseline, with no increase in abscesses or draining tunnels. “Partial response” was defined as at least 25% but less than 50% total AN reduction from baseline, with no increase in abscesses or draining tunnels. “Non-response” was defined as less than 25% total AN reduction and/or an increase in abscesses and/or draining tunnels.

In the base case, the response probabilities for active treatment (bimekizumab and secukinumab) varied across the initial treatment phase (first 16 weeks) and the maintenance phase. The response probabilities for best supportive care varied across the initial treatment phase (first 16 weeks), the first year of maintenance (16-48 weeks), and the remaining period until the end of the model (week 48+).

In the two active-treatment model arms (bimekizumab and secukinumab) a proportion of patients were assumed to discontinue from treatment. The cohort discontinuing active treatment received BSC, assuming the chance of either improvement or deterioration associated with BSC.

A transition to the absorbing “death” health state was assumed to be possible from any health state in the model.

Table 54 Features of the economic analysis

Factor	Previous evaluations		Current evaluation	
	TA392 [42]	TA935 [44]	Chosen values	Justification
Time horizon	Lifetime	Lifetime	Lifetime	Consistent with previous TAs
Treatment waning effect	N/A	N/A	N/A	N/A
Source of utilities	Based on EQ-5D index scores of adult patients enrolled in Phase III PIONEER II RCT [46] independent of treatments received (week 12 and week 36 data)	Health state utility values were derived based on EQ-5D-3L data sourced from the SUNSHINE [48] and SUNRISE [48] trials; treatment-specific utility values are applied	Health state utility values were derived based on EQ-5D-3L data sourced from the BE HEARD I [113] and BE HEARD II [114] trials; the model used different health state utility values for patients on active treatment vs BSC	Consistent with previous TAs
Source of costs	NHS Reference cost 2013–14 PSSRU 2014	National Schedule of NHS costs 2020–21 PSSRU 2021	National Schedule of NHS costs 2021–22 BNF 2023 PSSRU 2022	Consistent with previous TAs
Health effects measure	QALYs	QALYs	QALYs	Consistent with previous TAs
Half cycle correction	Yes	Yes	Yes	Consistent with previous TAs
Cycle length	4 weeks	4 weeks	4 weeks	Consistent with previous TAs

Abbreviations: BSC, best supportive case; BNF, British National Formulary; EQ-5D, 5-dimension EuroQol questionnaire; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; RCT, randomised controlled trial; TA, technology appraisal.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention (bimekizumab)

The base case used the following regimen for bimekizumab: 320 mg Q2W initial treatment up to week 16 followed by 320 mg Q4W maintenance treatment. This reflects the decision problem and the anticipated licence for bimekizumab. It also reflects the clinical trial evidence presented in section B.1.

In the initial treatment period, bimekizumab would be administered eight times, corresponding to cycles 1-4 in the economic model. After cycle 4 (post-week 16), a stopping rule was applied. The base case assumed that a proportion of the cohort failing at that point to achieve partial response (less than HiSCR25 [see Table 20]) would discontinue treatment and that they would initiate BSC as defined in section B.3.2.3.3. The remaining patients after week 16 would enter maintenance treatment.

All patients discontinuing maintenance treatment would receive BSC as defined in section B.3.2.3.3.

B.3.2.3.2 Secukinumab

The base case assumed 300 mg of secukinumab was administered by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing.

Based on clinical response, the marketing authorisation of secukinumab allows the monthly maintenance dose to be increased to 300 mg every 2 weeks (Q2W). The economic analysis did not consider this titration in the dose. There is no available evidence to inform the model of the corresponding efficacy after the titration. Although such a scenario was considered in TA935, it was not the scenario the committee based their final recommendations.

Two stopping rules were considered for patients on secukinumab:

- Stopping treatment at the end of the induction phase (week 16) for the proportion of patients in the non-response health state (less than HiSCR25).
- Stopping treatment in the maintenance phase for patients who remained in the non-response health state for 12 weeks (i.e. three consecutive model cycles).

After secukinumab treatment, patients were assumed to initiate BSC as defined in section B.3.2.3.3.

B.3.2.3.3 Best supportive care

Previous appraisals have discussed the uncertainty associated with the definition of BSC in the current NHS England clinical practice [42, 44]. In TA935 the manufacturer presented clinical expert opinion on the possible treatments associated with BSC. Based on that advice BSC was defined as biologics, topical antibiotics, oral antibiotics, dapsone, retinoids, ciclosporin and anti-androgens. The specific proportions of each treatment received by the average patient was discussed in TA935 and remain uncertain.

a) Biologic use in BSC

Although bimekizumab and secukinumab are evaluated in this analysis after the use of adalimumab, strong evidence suggests that patients in NHS England and Wales, continue on biologic treatment, despite lack of biologic efficacy. A prospective multinational survey of HS patients between October 2017 and July 2018, reported that a proportion continued on adalimumab despite failure to respond (Global VOICE study [20]). Furthermore, a consultant dermatologist practicing in England confirmed during an advisory board conducted by UCB that in the absence of alternative options, patients would continue with biologic treatment if they had a minimal level of response.

Following the above advice, the model used a balanced approach:

1. Placebo HiSCR data to reflect a lower response compared to efficacious active treatments (bimekizumab and secukinumab) and
2. A utility and cost to reflect accurately the use of adalimumab in current clinical practice in England and Wales

The probability of response to BSC was defined by the estimated RRs from the NMA and it is described in detail in B.3.3.2. The utility and cost of treatment with adalimumab, were applied to 20.8% of patients on BSC. The proportion was based on the frequency of biologic prescribed in Garg et. al 2020 [20].

b) Other treatments used in BSC

Other treatments, in addition or separate to adalimumab as discussed above in (a), that form BSC in NHS England and considered in TA935 were similar to the concomitant medication from BE HEARD I and II. Since concomitant medication is added already to all comparators, the model assumed no additional treatments for BSC.

B.3.3 Clinical parameters and variables

B.3.3.1 Cohort characteristics

A breakdown of baseline patient characteristics from BE HEARD I and II for all patients is presented in section B.2.3.3, Table 11. The CUA assumed the model cohort characteristics would reflect the average of the two clinical trials (Table 55) [131].

Table 55 CUA cohort characteristics

Input	Mean (SD)
Proportion female, n (%)	576 (57%)
Starting age, years	36.6 (12.2)
Weight, kg	97.3 (24.4)

Abbreviations: CUA, cost-utility analysis; kg, kilogram; SD, standard deviation.

B.3.3.2 Response to treatment

B.3.3.2.1 Initial period: from starting treatment to week 16

Treatment efficacy was represented by the proportion of patients achieving a HiSCR response level. The model allocated patients to five categories: “Very high response” (HiSCR90), “High response” (HiSCR75), “Response” (HiSCR50), “Partial response” (HiSCR25), and “Non-response” (HiSCR<25).

Individual patient data of 320mg bimekizumab Q2W (from both Q2W/Q2W and Q2W/Q4W trial arms) were analysed to derive fixed, 4-week transition probabilities. These probabilities were estimated using a generalised logit model (GLM) and informed by all 4-weekly transitions during the initial treatment period; from starting treatment to week 16.

Transition matrices were generated from the 4-week probabilities and were used in the economic model to derive the transitions of the bimekizumab cohort between HiSCR health states up to week 16. Subjects experiencing intercurrent events related to HS were considered non-responders (i.e., belonging to the ‘non-response’ state) following the intercurrent event; multiple imputation was used for all other missing data. Initiation of rescue systemic antibiotic use as determined by the principal investigator was defined as an

intercurrent event. Discontinuation due to adverse event or lack of efficacy also constituted an intercurrent event.

The baseline transition matrix (bimekizumab) is presented in Table 56.

Table 56 Four-week transition probabilities for bimekizumab by HiSCR score; initial treatment period weeks 0-16

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HiSCR: hidradenitis supprativa clinical response.
Note: values in each cell represent the probability of transitioning from the initial HiSCR score level to the final HiSCR level within a 4-week cycle.

To derive transition matrices for the comparators, we used the RRs of each comparator vs bimekizumab (reference) for HiSCR50, HiSCR75, and HiSCR90, as estimated in the NMA (section B.2.9).

Table 57 presents the method used to adjust the probabilities, where A, B, C, D, and E are the probabilities of transition to the Non-response, Partial response, Response, High response, and Very high response health states and r is the RR for HiSCR50, s is the RR for HiSCR75, and t is the RR for HiSCR90. As it was assumed that probabilities would be exclusive and exhaustive (A+B+C+D+E =1), additional constraints were applied to avoid implausible values.

Table 57 Application of RR to the transition matrix

Original values for a given starting state	Updated values
A	$\frac{[A-(C+D+E)*A*r]}{[A+B]}$
B	$\frac{[B-(C+D+E)*B*r]}{[A+B]}$
C	$(C+D+E)*r-(D+E)*s$
D	$(D+E)*s-E*t$
E	$E*t$

Abbreviations: RR, relative risk.

In the absence of evidence on RRs for HiSCR25 for secukinumab, the ratio of the updated values for transitions to the Non-response and Partial response health states was assumed to be the same as for the bimekizumab probability values.

For consistency, the same approach was followed for the BSC model arm by using the RR of placebo vs bimekizumab to generate the BSC transition matrix.

B.3.3.2.2 Maintenance: week 16 to week 48

The analysis conducted on the initial treatment period data (GLM on 4-weekly transitions) was repeated to derive transition probability matrices for bimekizumab Q2W/Q4W for the maintenance treatment period from week 16 to week 48 (Table 58). The analysis included only data from patients with at least a partial response (HiSCR25) at week 16.

Table 58 Four-week transition probabilities for bimekizumab (Q2W/Q4W) by HiSCR score category in weeks 16-48.

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HiSCR: hidradenitis suppurativa clinical response; Q2W, every 2 weeks; Q4W, every 4 weeks.
Note: values in each cell represent the probability of transitioning from the initial HiSCR score level to the final HiSCR level within a 4-week cycle.

The estimated RRs from the NMA in the initial treatment phase (at week 12/16[1]) were applied to the bimekizumab transition probabilities to derive the transition matrix for secukinumab.

The long-term response of patients in BSC was discussed in TA935 [44]. Clinical experts who advised the committee suggested that it was not likely to expect an improvement in the patient condition on HS. UCB conducted an advisory board of practicing dermatologists in England who also suggested that an improvement of HS in BSC was unlikely.

In line with the above opinion, for the cohort on BSC in the period 16-48 weeks, the base case analysis assumes a gradual deterioration of response. Under this assumption, patients cannot improve from their current state to a higher HiSCR response level. The probabilities of remaining in the current state, or transitioning to a worse state, were informed by the week 0-16 transition matrices derived from the placebo arm of BE HEARD I and II. This ensured the model reflected the condition and transitions observed in the placebo arm of the trial.

Table 59 Four-week transition probabilities for BSC by HiSCR for the period 16–48 weeks

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	1	0	0	0	0
HiSCR 25-<50	[redacted]	[redacted]	0	0	0
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	0	0

[1] In addition to the BE HEARD I and II trials that report data at week 16, the NMA includes evidence from the phase 2 trial of bimekizumab, which contributes with data at week 12.

HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	0
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; HiSCR: hidradenitis suppurative clinical response.
Note: values in each cell represent the probability of transitioning from the initial HiSCR score level to the final HiSCR level within a 4-week cycle.

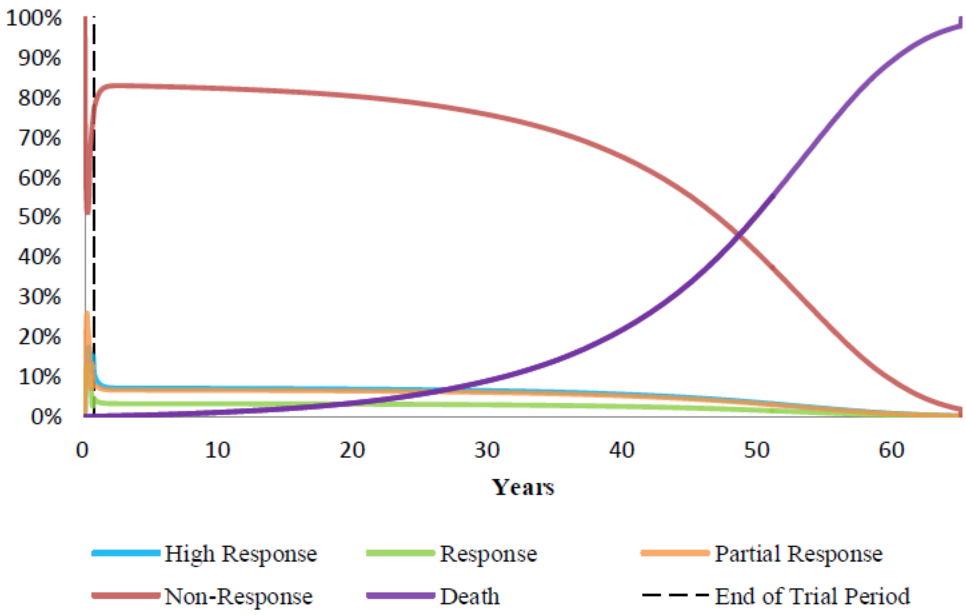
Sensitivity analysis considered alternative scenarios for the transition probabilities of BSC (B.3.10.3).

B.3.3.2.3 Long-term effectiveness: after week 48

After week 48, in the absence of long-term evidence on the durability of response the model used the transition probabilities from the 16-48-week analysis for bimekizumab (baseline) and secukinumab (RR from the NMA; section B.2.9.2). Sensitivity analysis (B.3.10.3) used the RR of secukinumab vs bimekizumab from the MAIC analysis to inform the transition probabilities for weeks 48+ (section B.2.9.4), applied on the 16-48 week baseline probabilities of bimekizumab. For BSC, retaining the same probabilities as in the period 16-48 week would suggest that in the long-term patients would stay on BSC treatment, while non response was achieved. In TA392 a plateau of treatment response was modelled for patients on supportive care (Figure 30).

In the absence of better evidence, this analysis adopted the same assumption after 48 weeks for BSC. This assumption was applied to all patients on BSC whether they would have started in the BSC comparator arm or following discontinuation from one of the active treatments.

Figure 30 Base case Supportive Care Markov trace of health states over time (reproduced from TA392 – manufacturer's submission [42])



Abbreviations: TA, technology appraisal.
SEC, secukinumab.

B.3.3.3 All-cause discontinuation from treatment during maintenance

In addition to response-related stopping rules, patients on treatment were at risk of discontinuing and receiving BSC due to any reason.

In the period 16-48 weeks a risk was calculated from the cases observed in BE HEARD I and II in the bimekizumab Q2W/Q4W arm and applied to all patients on treatment, irrespective of their response category (health-state membership). From [redacted] patients starting maintenance after at least partial response, [redacted] discontinued the study during the maintenance treatment period; a constant risk of [redacted] over a 4-week cycle. In the absence of evidence for secukinumab, the same discontinuation risk was used.

Beyond week 48, the discontinuation risk was set at 0.47% per 4-week cycle which is consistent with the value used in TA935 (sourced from Corbett et al. 2016) [161].

B.3.3.4 Adverse events

Overall, the results of the safety analysis on the BE HEARD clinical trials were consistent with the findings about the safety of bimekizumab in plaque psoriasis, psoriatic arthritis and axial spondyloarthritis [150, 151, 154, 155, 162]. Despite an increased incidence in oral candidiasis for patients on bimekizumab compared with placebo, most cases were mild to moderate and did not lead to discontinuation (see section B.2.10.2). As the events are mild in nature and typically easily resolved with simple management using over the counter treatments such as anti-inflammatory and anti-fungal medications, the base case did not include any costs or disutility.

A sensitivity analysis presented in B.3.10.3 included AEs to explore the impact of these events to the cost-utility results.

B.3.3.5 Mortality

A retrospective population-based cohort study from Korea was published in 2022 and it used data from the Nationwide Health Insurance Service database and the National Death Registry to present all-cause and cause-specific mortality risks among patients with HS [75]. The study reported a HR of 1.861 (CI 1.408, 2.461) for patients who underwent surgical procedures (Supplementary material 5 in [75]). The authors noted that patients who underwent surgery were more likely to have more severe HS and so the HR of 1.861 was considered an appropriate proxy for the model population. The model used the risk for the increased mortality of patients in the non-response state. The mortality risk for HS non-response patients was calculated as follows: $P_{HS}=1-\exp(-HR*(-\ln(1-P_{general})))$.

Patients in all other states were assumed to have the same risk as the general population.

The general population mortality was informed by national UK life tables [163]. To derive the risk for each model cycle, the age-specific mortality rate was weighted by the proportion of

male (43.2%) and female (56.8%) patients in the BE HEARD I and BE HEARD II clinical trials.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

B.3.4.1.1 Data analysis for use in the economic model

The clinical trials BE HEARD I and BE HEARD II collected EQ-5D-3L data. Least-square mean utility estimates were obtained from repeated measure analysis of covariance (ANCOVA) models on the BE HEARD trial data. All models included EQ-5D utility score (UK tariff [164]) as the outcome and at a minimum included the HiSCR response state and sex as a factor, as well as age and baseline EQ-5D utility score as covariates.

Regarding data collected in the initial treatment period (weeks 0–16), in addition to the predictors listed above the models included treatment (placebo, bimekizumab Q2W, bimekizumab Q4W) as a factor, along with an interaction term between treatment and the HiSCR response level. The utility values for each HiSCR category were based on the least square mean estimate for each combination of treatment and HiSCR response. The analysis used observed case data across the entirety of the contributing period. The results of the analysis are presented in Table 60.

Table 60 BE HEARD I and BE HEARD II analysis of EQ-5D-3L

Response health state	BKZ LS mean (SE)	Placebo LS mean (SE)
Initial treatment period		
Non response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Response	[redacted]	[redacted]
High response	[redacted]	[redacted]
Very high response	[redacted]	[redacted]
Maintenance treatment period		
Non response	[redacted]	N/A
Partial response	[redacted]	N/A
Response	[redacted]	N/A
High response	[redacted]	N/A
Very high response	[redacted]	N/A

Note: BKZ initial treatment: informed by pooled BKZ Q2W arms up to week 16; BKZ maintenance treatment: pooled analysis informed by all BKZ arms in maintenance phase (including placebo-BZK Q2W subjects).
Abbreviations: BKZ, bimekizumab; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; LS, least-squares; N/A, not applicable; SE, standard error.

B.3.4.1.2 Justification of treatment-related utility values

In TA935 the manufacturer presented strong statistical evidence in support of treatment-specific utilities, with statistically significant differences between secukinumab Q2W and

Q4W pooled and placebo observed in each HiSCR category with the exception of high response [44].

To explore the appropriateness of this assumption across all HiSCR response states, based on data from BE HEARD I and II, additional repeated measures ANCOVA models were run, similar to those described above. The models used all data from weeks 0 to 16 from BE HEARD I and II and contained an interaction term between treatment and HiSCR response state in addition to the minimum set of predictors. All analyses were based on observed case data only, irrespective of the occurrence of intercurrent events.

The p-values generated by the post-hoc analyses were nominal and intended for exploratory insight (Table 61). The model coefficients from the additional repeated measures ANCOVA models described above are presented in Table 61 for the separate bimekizumab arms and Table 62 for the pooled bimekizumab arms. Particular interest lies in the coefficients for the interaction terms between treatment and HiSCR response state. Coefficients for bimekizumab Q2W and bimekizumab Q4W were obtained from a model where treatment was coded as a factor with three levels (placebo, bimekizumab 320 mg Q2W and bimekizumab 320 mg Q4W); coefficients for BKZ total were sourced from a model where treatment was coded as a factor with two levels (placebo and bimekizumab total [where the 2 separate bimekizumab dosing regimens received during the first 16 weeks of BE HEARD I and II, i.e. Q2W and Q4W, were combined]). In each case, placebo was used as the reference level for treatment and thus, for a given HiSCR response state, the model coefficients corresponded to the difference in utility, relative to placebo, for each treatment arm.

Table 61 Repeated Measures ANCOVA Model Coefficients (Separate BKZ Arms)

		Fixed effect	Estimate	SE	p-value
		Intercept	[redacted]	[redacted]	[redacted]
Baseline EQ-5D Utility (UK Tariff)		Baseline EQ-5D Utility	[redacted]	[redacted]	[redacted]
Age		Age	[redacted]	[redacted]	[redacted]
Sex (Reference Category: Male)		Female	[redacted]	[redacted]	[redacted]
Response State (Reference Category: Non-Response)		Partial Response	[redacted]	[redacted]	[redacted]
		Response	[redacted]	[redacted]	[redacted]
		High Response	[redacted]	[redacted]	[redacted]
		Very High Response	[redacted]	[redacted]	[redacted]
Interaction Between Treatment and Response State	BKZ Q4W (Reference Arm: Placebo)	Non-Response	[redacted]	[redacted]	[redacted]
		Partial Response	[redacted]	[redacted]	[redacted]
		Response	[redacted]	[redacted]	[redacted]
		High Response	[redacted]	[redacted]	[redacted]
		Very High Response	[redacted]	[redacted]	[redacted]
	BKZ Q2W (Reference Arm: Placebo)	Non-Response	[redacted]	[redacted]	[redacted]
		Partial Response	[redacted]	[redacted]	[redacted]
		Response	[redacted]	[redacted]	[redacted]
		High Response	[redacted]	[redacted]	[redacted]
		Very High Response	[redacted]	[redacted]	[redacted]

Abbreviations: ANCOVA, analysis of covariance; BKZ, bimekizumab; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error; UK, United Kingdom.

Table 62 Repeated Measures ANCOVA Model Coefficients (Pooled BKZ Arms)

	Fixed Effect	Estimate	SE	p-value
	Intercept	[redacted]	[redacted]	[redacted]
Baseline EQ-5D Utility (UK Tariff)	Baseline EQ-5D Utility	[redacted]	[redacted]	[redacted]
Age	Age	[redacted]	[redacted]	[redacted]
Sex (Reference Category: Male)	Female	[redacted]	[redacted]	[redacted]
Response State (Reference Category: Non-Response)	Partial Response	[redacted]	[redacted]	[redacted]
	Response	[redacted]	[redacted]	[redacted]
	High Response	[redacted]	[redacted]	[redacted]
	Very High Response	[redacted]	[redacted]	[redacted]
Interaction Between Treatment and Response State BKZ Total (Reference Arm: Placebo)	Non-Response	[redacted]	[redacted]	[redacted]
	Partial Response	[redacted]	[redacted]	[redacted]
	Response	[redacted]	[redacted]	[redacted]
	High Response	[redacted]	[redacted]	[redacted]
	Very High Response	[redacted]	[redacted]	[redacted]

Abbreviations: ANCOVA, analysis of covariance; BKZ, bimekizumab; SE, standard error; UK, United Kingdom.

In both cases, all model coefficients for the interactions were positive, reflecting a higher estimated utility for patients treated with BKZ for all health states. Strong evidence for treatment-specific utilities was found for the non-response health state (BKZ total: p-value = [redacted], BKZ Q2W: p-value = [redacted], BKZ Q4W: p-value = [redacted]) and the high response health state (BKZ total: p-value = [redacted], BKZ Q2W: p-value = [redacted]).

Overall, the evidence across multiple sources supports using treatment-specific utility values in the analysis. In TA935, utility analyses from two clinical trials support that there are differences in utility values between treatment and BSC [44]. Further analysis from the BE HEARD I and II studies consistently showed positive interactions across all health states for patients treated with bimekizumab, including reliable evidence in the non-response health state.

B.3.4.2 Mapping

No mapping was conducted to derive health state utility values.

B.3.4.3 Health-related quality-of-life studies

Identification of relevant HRQoL studies was conducted via an SLR, updated on 6 November 2023, and described in detail in Appendix H. The results of studies using generic instruments to assess the impact of HS are described in Appendix H.1.3.2, Table 145.

B.3.4.4 Adverse reactions

The base case did not include AEs (see section B.3.3.4). In section B.3.10.3 sensitivity analysis was conducted to include disutility of events.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The base case used the results of the analysis conducted on BE HEARD I and BE HEARD II to populate the utility values. Different utility values were used for the initial and maintenance treatment periods. These utility values supported that quality of life improves over time while on treatment and that, consistent with treatment-related utilities from SUNRISE and SUNSHINE [44], that there is a numerical quality of life benefit to being on an active therapy (see Table 61 and Table 62). The utility values for secukinumab were set the same as those for bimekizumab, in the absence of evidence supporting differential utilities between active therapies.

The utility values for patients on BSC during induction used treatment specific utilities from the placebo EQ-5D-3L data (0–16 weeks). In the maintenance phase the utility values applied to the cohort on BSC were weighted based on a proportion of patients receiving adalimumab. To inform the proportion of patients on biologic therapy in BSC, we used biologic prescribing in the Global VOICE study [20], a multinational HS study, and validated the assumption with an external clinical advisor. Further description of the weighting is described below:

- for 79.2% of the cohort, the BE HEARD trial placebo group EQ-5D-3L data (0–16 weeks).
- for 20.8% of the cohort (patients receiving biologic treatment; see section B.3.2.3.3), the utility values from the BE HEARD I and II bimekizumab maintenance treatment; that is, data from a pooled analysis informed by all bimekizumab arms in maintenance phase (including placebo-bimekizumab Q2W subjects).

All the utility estimates associated with response were adjusted to account for the impact of age on patients' HRQoL. The UK general population utility estimate reported by Hernández Alava et al. (2022) [165] was used to fix a base index utility for individuals matching the BE HEARD trial population. The adjustment for consecutive years in the model involved dividing the general population utility value for each age group by the base index utility. Sensitivity analysis assumed no age adjustment to the utilities.

Table 63 Summary of utility values for cost-effectiveness analysis

Analysis, treatment or event and treatment phase	State	Utility value: mean (standard error)	Reference in submission	Justification
Initial treatment period for bimekizumab or secukinumab	Non response	[redacted]	B.3.4.5 (p 140)	Collected data from the clinical trial BE HEARD I and II were used. In the absence of data for secukinumab, the same utility values were assumed.
	Partial response	[redacted]		
	Response	[redacted]		
	High response	[redacted]		
	Very high response	[redacted]		
Maintenance with bimekizumab or secukinumab	Non response	[redacted]		
	Partial response	[redacted]		
	Response	[redacted]		
	High response	[redacted]		
	Very high response	[redacted]		
First 16 weeks in BSC	Non response	[redacted]	B.3.4.5 (p 140)	Collected data from the clinical trial BE HEARD I and II were used.
	Partial response	[redacted]		
	Response	[redacted]		
	High response	[redacted]		
	Very high response	[redacted]		
After 16 weeks in BSC[a]	Non response	[redacted]	B.3.4.5 (p 140)	Placebo utility data from BE HEARD were weighted for the proportion of patients, assumed to continue use of adalimumab .
	Partial response	[redacted]		
	Response	[redacted]		
	High response	[redacted]		
	Very high response	[redacted]		

[a] Precision of these estimates was based on the individual utility values from placebo initial treatment (0-16 weeks) and BKZ maintenance treatment: pooled analysis informed by all BKZ arms in maintenance phase (including placebo-BZK Q2W subjects).
Source: BE HEARD I and II [113, 114]
Abbreviations: BSC, best supportive care.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify relevant cost and resource use data for adult patients with moderate-to-severe HS, as described in Appendix I. The review identified 21 studies, two of which reported evidence from the UK [88, 166]. Both studies presented resource use for patients with HS in England (Hospital Episode Statistics). The response states, as defined by HiSCR levels reported in the identified studies, did not align with the mutually exclusive health states of this cost-utility analysis. Therefore, it was concluded that the literature review did not yield any source that was deemed more appropriate than previously published TAs TA932 and TA935.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs were obtained from the British National Formulary (BNF) [167].

The list price of bimekizumab is £2,443 per 320 mg dose (2 × 160 mg prefilled syringes). The company has a commercial arrangement which makes bimekizumab available to the NHS with a discount. The dose for bimekizumab is 16 weeks of initial therapy of 320 mg every 2 weeks (Q2W) followed by maintenance therapy 320 mg every 4 weeks.

The list price of secukinumab is £1,218.78 per 300 mg/2 ml pre-filled pen, or per 2 x 150 mg/1 ml pre-filled injection pens. The company has a commercial arrangement which makes secukinumab available to the NHS with a discount. The size of the discount is commercial in confidence. The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing.

Use of adalimumab biosimilar was assumed for patients on BSC (20.8%) [20]. The lowest available adalimumab biosimilar has a cost of £633.60 (Amgevita®) for a 40 mg prefilled pen or syringe and for a 40 mg/0.8 ml vial. The recommended dose of adalimumab for people with HS is 160 mg on day 1 (given as 4 injections in 1 day or as 2 injections each day for 2 consecutive days), 80 mg on day 15 (given as 2 injections in 1 day), and a single 40 mg injection every week from week 4 onwards (QW).

Drug acquisition costs were calculated per cycle (4 weeks) based on the dose regimen of each drug. Table 64 shows the number of administrations and the drug acquisition costs per cycle.

The administration cost of a subcutaneous injection was assumed to be £47.39, for a one-hour nurse visit (Band 6) [168]. It was assumed that the administration cost would apply only for the first injection, and patients would self-administer subsequent doses of the drugs.

Table 64 Number of administrations, acquisition and administration costs at different model cycles separated by initial treatment phase and maintenance phase

	First model cycle	Cycle 2, 3, 4 in the model	Maintenance cycles
Number of administrations			
BKZ: 16 weeks of initial therapy 320 mg every 2 weeks (Q2W) followed by maintenance therapy 320 mg every 4 weeks.	2	2	1
SEC: 300 mg initial dosing at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing (Q4W)	5	0.9199	0.9199
ADA (part of BSC): 160 mg on day 1, 80 mg on day 15, and a single 40 mg injection every week from week 4 onwards (QW).	6 x 40 mg	4	4
Acquisition costs			
BKZ 320 mg Q2W/Q4W (w/ PAS)	[redacted]	[redacted]	[redacted]
SEC 300 mg Q4W	£6,093.90	£1,121.18	£1,121.18
ADA 40 mg (part of BSC)	£1,900.80	£1,267.20	£1,267.20
BSC (20.8% receiving ADA)	£397.95	£266.17	£266.17
Administration costs			
BKZ 320 mg Q2W/Q4W SEC 300 mg Q4W/Q2W ADA 40 mg (part of BSC)	1 hour nurse visit (£47.39) for the first injection.	The model assumed patients self-administer subsequent injections.	

Abbreviations: ADA, adalimumab; BKZ, bimekizumab; BSC, best supportive care; mg, milligram; PAS, patient access scheme; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab.

B.3.5.1.1 Concomitant medication acquisition cost

The concomitant medication use in the base case was informed by treatment use in BE HEARD I and II [113, 114]. Table 65 describes the dosing regimens, formulation information, acquisition costs and percent uptake as informed by the clinical trials.

Table 65 Concomitant medication in the economic model

Generic name	Drug dose and regimen	Strength per unit (mg or mL)	Pack size	Pack price (£)	Unit cost source	Use in clinical trial *
Ibuprofen	0.6 g daily	600	84	£1.77	Department of Health and Social Care (eMIT) (2023) [169]	13.72%
Paracetamol	4 g daily	500	100	£2.80	Department of Health and Social Care (eMIT) (2023) [169]	16.21%
Doxycycline 100 mg	100 mg twice daily	100	1	£0.12	NHSBSA (2023) for code 0501030I0AAABAB [170]	7.95%
Metformin	500 mg twice daily	250 mg	28	£0.33	Department of Health and Social Care (eMIT) (2023) [169]	6.16%
Omeprazole	20 mg once daily	20 mg	28	£0.35	Department of Health and Social Care (eMIT) (2023) [169]	2.88%
Colecalciferol	800iu once daily	800 units	30	£1.26	Department of Health and Social Care (eMIT) (2023) [169]	2.28%

Generic name	Drug dose and regimen	Strength per unit (mg or mL)	Pack size	Pack price (£)	Unit cost source	Use in clinical trial *
Fluconazole	150 mg once per cycle	150 mg	1	£0.35	Department of Health and Social Care (eMIT) (2023) [169]	5.96%
Amoxicillin	500 mg three times daily	250 mg	21	£0.47	Department of Health and Social Care (eMIT) (2023) [169]	1.69%
Levonorgestrel	150 µg once daily for 21 days	150 µg	63	£1.13	Department of Health and Social Care (eMIT) (2023) [169]	3.77%
Drospirenone; ethinylestradiol	3 mg once daily for 21 days	3 mg	63	£5.67	Department of Health and Social Care (eMIT) (2023) [169]	1.49%
Levothyroxine sodium	100 µg once daily	50 µg	28	£0.34	Department of Health and Social Care (eMIT) (2023) [169]	1.79%
Salbutamol	4 mg 3.5 times daily	100 µg	200	£1.40	Department of Health and Social Care (eMIT) (2023) [169]	2.68%
mRNA COVID vaccine	Not included					3.57%
Tozinameran COVID vaccine	Not included					16.09%

*Source: BE HEARD I and II [113, 114].
Abbreviations: g, gram; mg, milligram; mL, millilitre; µg, microgram.

B.3.5.2 Health-state unit costs and resource use

Consistent with TA392, and TA935, the estimates for healthcare resource utilisation (HCRU) in the model was informed by a physician survey that described the burden by HiSCR response level [42, 44].

To populate the level of resource use for patients with “Very high response” (HiSCR90), an adjustment was necessary by fitting a parametric model. For each resource use item, an increasing trend in mean HCRU with a decreasing HiSCR response was observed. Two types of trendlines in Microsoft Excel® were used to fit the mean resource use by HiSCR response (using the midpoint percentage):

1. polynomial degree 2,
2. logarithmic parametric.

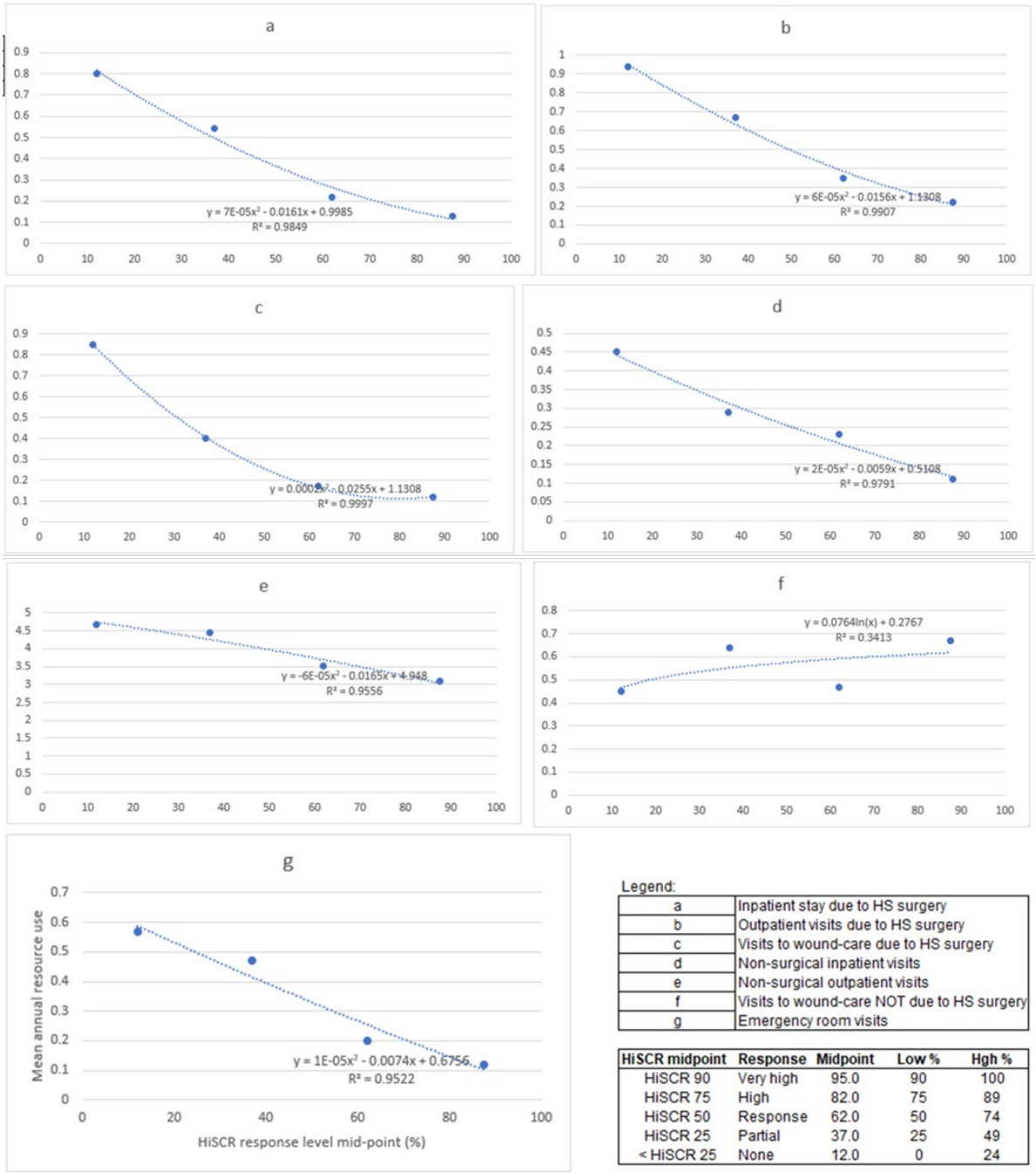
Scatter plots with trendlines and equations are shown in Figure 31. The model with the highest value of R^2 was selected to predict the mean annual HCRU in the ‘Very high response’ (HiSCR90) category and the revised ‘High response’ (HiSCR75) category. The HCRU in categories “Response”, “Partial response”, and “Non-response” were set as in TA392 [42], adjusted to severity in BE HEARD I and II.

Sensitivity analysis assumed that the 'Very high response' (HiSCR90) category has the same resource use as HiSCR75 and no adjustment was assumed for the lower categories; values were as reported in TA392 [42].

Table 66 presents the results of the HCRU analysis with the seven components of NHS resources impacted by the level of HiSCR response.

The unit costs for each resource item (Table 67) were obtained from NHS Reference Costs. [171]

Figure 31 Parametric Fits of the Model to HCRU Values



Legend:

a	Inpatient stay due to HS surgery
b	Outpatient visits due to HS surgery
c	Visits to wound-care due to HS surgery
d	Non-surgical inpatient visits
e	Non-surgical outpatient visits
f	Visits to wound-care NOT due to HS surgery
g	Emergency room visits

HiSCR midpoint	Response	Midpoint	Low %	Hgh %
HiSCR 90	Very high	95.0	90	100
HiSCR 75	High	82.0	75	89
HiSCR 50	Response	62.0	50	74
HiSCR 25	Partial	37.0	25	49
< HiSCR 25	None	12.0	0	24

.Abbreviations: HCRU, healthcare resource utilisation; HiSCR, hidradenitis suppurativa clinical response; HS, hidradenitis suppurativa.

Table 66 Annual Resource Use per Health State (from TA392 adjusted to severity in BE HEARD I and II)

Resource	Annual resource use per health state				
	Non response	Partial response	Response	High response	Very high response
Hospitalisations for HS surgery	0.80	0.49	0.21	0.14	0.11
Outpatient visits due to HS surgery	0.92	0.63	0.35	0.23	0.17
Visits to wound care due to HS surgery	0.76	0.37	0.18	0.11	0.13
Hospitalisations, non-surgery related	0.46	0.27	0.21	0.13	0.11
Routine outpatient visits	4.67	4.38	3.51	3.17	2.83
Visits to wound care not due to HS surgery	0.45	0.66	0.52	0.68	0.70
A&E visits	0.58	0.45	0.21	0.14	0.07

Abbreviations: A&E, accident and emergency department; HS, hidradenitis suppurativa.
Source: BE HEARD I and BE HEARD II [113, 114] and parametric fit.

Table 67 Unit costs by resource type

Resource	Unit cost (£)	Comments
Hospitalisations for HS surgery	2,982.10	Weighted average: JC40Z (elective), JC41Z (elective), JC42C (elective), and JC43C (elective)
Outpatient visits due to HS surgery	152.30	Total outpatient attendance, HRG code: 330, total
Visits to wound care due to HS surgery	152.30	Total outpatient attendance, HRG code: 330, total
Hospitalisations, non-surgery related	1,654.30	Weighted average: JD07D (elective patients) and JD07K (elective patients)
Routine outpatient visits	152.30	Total outpatient attendance, HRG code: 330, total
Visits to wound care not due to HS surgery	152.30	Total outpatient attendance, HRG code: 330, total
A&E visits	278.10	Total HRGs, weighted average: VB01Z–VB09Z

Abbreviations: A&E, accident and emergency department; HRG, healthcare resource group; HS, hidradenitis suppurativa; NHS, National Health Service.
Note: Costs were calculated by taking a weighted average of unit costs and the associated activity reported.
Source: NHS [171].

B.3.5.3 Adverse reaction unit costs and resource use

The base case did not include AEs (see section B.3.3.4). In section B.3.10.3 sensitivity analysis was conducted to include cost of events.

B.3.5.4 Miscellaneous unit costs and resource use

No further costs or resource use were included in the analysis.

B.3.6 Severity

The technology does not meet the criteria for a severity weight.

B.3.7 Uncertainty

HS is a condition that can vary widely in severity and symptoms. This complexity introduces uncertainty in estimating patients' quality of life and use of NHS resources. The clinical trials provide a robust framework for evaluating the treatments' short-term efficacy and safety (bimekizumab and secukinumab). However, outcomes are not available over the lifetime of the patients, so an extrapolation of results to predict long-term outcomes is needed, resulting in increased economic model uncertainty. The dynamic and unpredictable course of HS in the long-term, characterised by fluctuating symptoms, variable standard of care, and variable response to treatments, further complicates extrapolation.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of the variables used in the economic model is presented in Table 68.

Table 68 Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Probabilistic analysis: Precision shown as confidence interval or SE (distribution)	Reference to section in submission
Model properties			
Time horizon	Lifetime	N/A	**B.3.2.2**
Cycle length	4 weeks	N/A	**B.3.2.2**
Half-cycle correction	Yes	N/A	**B.3.2.2**
Discount rate, costs and effectiveness	3.5%	N/A	**B.3.2.2**
Perspective on cost	NHS and PSS	N/A	**B.3.2**
Perspective on outcomes	All relevant health affects	N/A	**B.3.2**
Mortality risk	General population mortality applied to all health states except non response. Hazard ratio of 1.861 applied for patients in the non-response state.	HR CI: 1.408-2.461 (Lognormal)	**B.3.3.5**
Age-adjusted utility	Yes	N/A	**B.3.3.5**
Patient characteristics			
Age, years	36.6	N/A	**B.3.3**
Sex: female (%)	57%	N/A	**B.3.3**
Weight (mean kg)	97.3	N/A	**B.3.3**
Efficacy			

Variable		Value (reference to appropriate table or figure in submission)	Probabilistic analysis: Precision shown as confidence interval or SE (distribution)	Reference to section in submission
Transition probabilities of BKZ		Three sets of transition probabilities are used in model: Induction phase (0-16 weeks) Maintenance phase (week 16 until the end))	Transition probabilities sampled from a gamma distribution using the Dirichlet method in the absence of variance-covariance data	**B.3.3.2**
Comparative effectiveness for SEC	RR of ≥HiSCR50	[redacted]	[redacted]	**B.3.3.2**
	RR of ≥HiSCR75	[redacted]	[redacted]	
	RR of ≥HiSCR90	[redacted]	[redacted]	
Comparative effectiveness for BSC	RR of ≥HiSCR50	[redacted]	[redacted]	**B.3.3.2**
	RR of ≥HiSCR75	[redacted]	[redacted]	
	RR of ≥HiSCR90	[redacted]	[redacted]	
Discontinuation				
Discontinuation rates (per cycle) for BKZ in year 1		[redacted]	Alpha: [redacted] Beta: [redacted] (Beta)	**B.3.3.3**
Discontinuation rates (per cycle) for BKZ in years 2+		[redacted]	Alpha: [redacted] Beta: [redacted] (Beta)	**B.3.3.3**
Utilities				
Initial treatment period BKZ or SEC	Non response	[redacted]	0.722-0.761 (Beta)	**B.3.4.1**
	Partial response	[redacted]	To retain correlation across the HSUVs, we sampled the proportionate difference in the deterministic values between this health state and non-response and added the benefit to the sampled non-response value. (Lognormal)	
	Response	[redacted]		
	High response	[redacted]		
	Very high response	[redacted]		
Maintenance BKZ or SEC	Non response	[redacted]	0.735-0.780 (Beta)	**B.3.4.1**
	Partial response	[redacted]	To retain correlation across the HSUVs,	

Variable		Value (reference to appropriate table or figure in submission)	Probabilistic analysis: Precision shown as confidence interval or SE (distribution)	Reference to section in submission
	Response	[redacted]	we sampled the proportionate difference in the deterministic values between this health state and non-response and added the benefit to the sampled non-response value. (Lognormal)	
	High response	[redacted]		
	Very high response	[redacted]		
BSC first 16 weeks	Non response	[redacted]	0.632-0.713 (Beta)	**B.3.4.1**
	Partial response	[redacted]	To retain correlation across the HSUVs, we sampled the proportionate difference in the deterministic values between this health state and non-response and added the benefit to the sampled non-response value. (Lognormal)	
	Response	[redacted]		
	High response	[redacted]		
	Very high response	[redacted]		
BSC from week 16 until the end of the model	Non response	[redacted]	Sampling of the post-16 week utility values for BSC was based on the individual utility value components: placebo initial treatment (0-16 weeks) and BKZ maintenance treatment, that is, pooled analysis informed by all BKZ arms in maintenance phase (including placebo-BZK Q2W subjects).	**B.3.4.5**
	Partial response	[redacted]		
	Response	[redacted]		
	High response	[redacted]		
	Very high response	[redacted]		
Disease management costs				
Acquisition cost: BKZ 320 mg		PAS price: [redacted]	N/A	**B.3.5.1**
Acquisition cost: SEC 300 mg		List price: £1,219.00	N/A	**B.3.5.1**
Acquisition cost: adalimumab (amgevita)		(2x 40 mg): £633.60	N/A	**B.3.5.1**
First administration cost for subcutaneous drugs		£47.39	Assumed SE of 10% of deterministic value (Gamma)	**B.3.5.1**
Concomitant medication: ibuprofen		£1.77 per pack	N/A	**B.3.5.1**
Concomitant medication: paracetamol		£2.80 per pack	N/A	**B.3.5.1**

Variable	Value (reference to appropriate table or figure in submission)	Probabilistic analysis: Precision shown as confidence interval or SE (distribution)	Reference to section in submission
Concomitant medication: doxycycline	£0.12 per pack	N/A	**B.3.5.1**
Concomitant medication: Metformin	£0.33 per pack	N/A	**B.3.5.1**
Concomitant medication: Omeprazole	£0.35 per pack	N/A	**B.3.5.1**
Concomitant medication: Colecalciferol	£1.26 per pack	N/A	**B.3.5.1**
Concomitant medication: Fluconazole	£0.35 per pack	N/A	**B.3.5.1**
Concomitant medication: Amoxicillin	£0.47 per pack	N/A	**B.3.5.1**
Concomitant medication: Levonorgestrel	£1.13 per pack	N/A	**B.3.5.1**
Concomitant medication: Drospirenone; ethinylestradiol	£5.67 per pack	N/A	**B.3.5.1**
Concomitant medication: Levothyroxine sodium	£0.34 per pack	N/A	**B.3.5.1**
Concomitant medication: Salbutamol	£1.40 per pack	N/A	**B.3.5.1**
Resource use	Annual resource use for each HiSCR level was separated into seven healthcare type categories.	N/A	**B.3.5.2**
Hospitalisations for HS surgery	£2,982.10	Assumed SE of 10% of deterministic value (Gamma) [a]	**B.3.5.2**
Outpatient visits due to HS surgery	£152.30	Assumed SE of 10% of mean value (Gamma)	**B.3.5.2**
Visits to wound care due to HS surgery	£152.30	Assumed SE of 10% of mean value (Gamma)	**B.3.5.2**
Hospitalisations non-surgery related	£1,654.30	Assumed SE of 10% of mean value (Gamma)	**B.3.5.2**
Routine outpatient visits	£152.30	Assumed SE of 10% of mean value (Gamma)	**B.3.5.2**
Visits to wound care not due to HS surgery	£152.30	Assumed SE of 10% of mean value (Gamma)	**B.3.5.2**
A&E visits	£278.10	Assumed SE of 10% of mean value (Gamma)	**B.3.5.2**

[a] Precision was based on an assumption due to the mean being calculated from a weighted average of several codes.
Abbreviations: A&E, Accident and Emergency; BKZ, bimekizumab; BSC, best supportive case; CI, confidence interval; HiSCR, Hidradenitis Suppurativa Clinical Response; HR, hazard ratio; HS, hidradenitis suppurativa; HSUVs, health state utility values; kg, kilogram; mg, milligram; N/A, not available; NHS, National Health Service; NR, not reported; PAS, patient access scheme; PSS, patient support services; SE, standard error.

B.3.8.2 Assumptions

In Table 69 there is a brief summary of all the assumptions in the base case analysis, and their justification.

Table 69 List of assumptions for the base case analysis

	Description of base case assumption	Justification
Extension of response categories to capture HiSCR90	The patient cohort was allocated across six health states: five based on their response to treatment and death. Compared with previous model structures in TA392 and TA935, an additional response category ("Very high response" - HiSCR90) was introduced.	By extending the response categories and separating high response to over HiSCR75 and HiSCR90, the model reflects the clinical findings of BE HEARD I and II more accurately.
Dose regimen of SEC	The base case assumed a stable maintenance dose for SEC (Q4W), despite titration being part of its marketing authorisation (Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks.)	UCB has no evidence of the efficacy of the higher maintenance dose. Based on the secukinumab PAS, the manufacturer would make available to the NHS more frequent doses at the same price as once per month. Therefore, there would be no additional cost for titrated patients in the NHS.
Definition of BSC and use of biological treatment	A balanced approach was used in the model to reflect clinical practice in England and Wales: 1. The HiSCR data of placebo patients and assumptions for deterioration were used for BSC to reflect a lower response compared to efficacious active treatments (BKZ and SEC) 2. A utility and cost reflecting adalimumab use, were applied to a proportion of BSC patients (20.8%).	There is strong evidence to support that patients, continue on biologic treatment, despite the lack of biologic efficacy. A prospective multinational survey of HS patients between October 2017 and July 2018, reported that a proportion continued on adalimumab despite failure to respond (Global VOICE study [20]). A consultant dermatologist practicing in England confirmed the trend.
Baseline transition probabilities: bimekizumab for the initial treatment period and up to week 48.	Observed patient transitions over 16 weeks were analysed using a GLM to generate fixed, 4-week transition probabilities for the baseline risk of treatment response for patients receiving bimekizumab. The analysis was repeated for patients with at least a partial response (continued treatment) for the period from week 16 until week 48.	The clinical trial data were the only source for patient response to BKZ and were used to inform patient transitions in the economic model.
Transition probabilities during the initial treatment period: SEC and BSC (up to 16 weeks)	To derive transition matrices for the comparators, the RRs for each comparator versus BKZ for HiSCR50, HiSCR75, and HiSCR90, as estimated in the NMA (section B.2.9), were used. The individual transition probabilities were further	In the absence of direct evidence of the response to SEC vs bimekizumab, the results of the NMA were used to derive the comparator transition matrices. Further adjustment was necessary to ensure the synthesis of the baseline risks with the NMA RRs

	Description of base case assumption	Justification
	adjusted to ensure probabilities were complete and exhaustive.	resulted in exhaustive and mutually exclusive probabilities. Since both the BKZ and SEC clinical trials had a placebo control arm in the NMA, the response to BSC was informed from the NMA estimates rather than directly from the BE HEARD I and II trials.
Maintenance efficacy for SEC	The RR from the NMA was applied to the transition probabilities from the 16–48-week analysis for BKZ (baseline) to derive the transition probabilities.	In the absence of direct evidence of the response to SEC vs bimekizumab, the same relative risk (compared with bimekizumab) that informed the initial treatment period was applied to the remaining treatment duration with SEC.
Efficacy with BSC post week 16	In the period 16-48 weeks, a "gradual deterioration" was assumed for the transition probabilities of the cohort on BSC; patients could remain in their current state but could not improve to a higher HiSCR response level. After week 48, it was assumed that BSC patients would remain stable in their response category level until the end of the model period.	Due to cross-over, the clinical trials did not provide evidence for the transitions of patients without active treatment. Clinical experts who advised the committee in TA 935 suggested that it was not likely to expect an improvement in the patient condition on HS. UCB conducted an advisory board of practicing dermatologists in England who also suggested that an improvement of HS in BSC was unlikely. For the period after week 48, the BKZ model adopted the plateaued response presented in TA 392 and consistent with EAG analyses conducted in TA935. Sensitivity analysis tested several alternative scenarios.
Discontinuation from treatment maintenance	The same discontinuation risk from treatment maintenance was applied to BKZ or SEC. For 16-48 weeks, the risk was calculated from the cases observed in BE HEARD I and II. Beyond week 48, a secondary source was used for the discontinuation risk was a secondary source.	As there was no comparative evidence on the risk of discontinuation between the two treatment options, and since the primary factor in treatment and health state allocation is the NMA on response, it was assumed that the risk of discontinuation due to any cause was equal for both options. The long-term discontinuation risk (after week 48) applied on both comparators is consistent with both TA935 and TA392.
No AEs for any model comparator	The base case did not consider AEs for any model comparator.	The assumption of no AEs for the active treatments is consistent with the approach taken in TA935. An increased incidence of oral candidiasis for patients on BKZ compared with placebo was observed in the clinical trials. However, most

	Description of base case assumption	Justification
		cases were mild to moderate and did not lead to discontinuation (see section B.2.10.2), suggesting no material effect in the economic model. Furthermore, the base case uses treatment-specific health state utility values. Therefore, any disutility from the adverse events would be included in the values used for bimekizumab.
Elevated mortality risk for non response	Patients in the "Non-response" health state were assumed to suffer an elevated mortality risk compared to the general population.	TA935 suggested that there could be an increased risk of mortality in patients with HS as compared with the general population [75]. This was not modelled at the time in the absence of data. In 2023 a prospective study reported evidence on all-cause and cause-specific mortality risks among patients with HS. This data informed the model for the mortality risk of patients with non response to treatment.
Treatment-related utility values	The model assumed different utility values for patients on active treatment (SEC or bimekizumab) vs patients without treatment (a proportion of the cohort on BSC).	In TA935 strong statistical evidence was presented in support of treatment-specific utilities, with statistically significant differences between SEC Q2W and Q4W pooled and placebo observed in each HiSCR category with the exception of high response. To explore the appropriateness of this assumption a post-hoc analysis of EQ-5D data from BE HEARD I and II was conducted. The result suggested higher estimated utility for patients treated with BKZ compared to placebo for all health states.
HRQL for BSC	The utility for a proportion of the cohort (20.8%) on BSC who continued on adalimumab despite inadequate response was assumed to be reflected by values observed for BKZ maintenance treatment: pooled analysis informed by all BKZ arms in maintenance phase (including placebo-BZK Q2W subjects)..	The base case assumed a treatment-related utility for the proportion of patients on adalimumab. A similar scenario was presented in TA935 but only for costs. Including effect on quality of life avoids biasing the analysis.
Adjustment of utility gains for age	The UK general population utility estimate reported by Hernández Alava et al. (2022) [165] was used to adjust the response-level utility estimates.	Consistent with the approach in TA935
Concomitant medication use	Concomitant medication from BE HEARD I and II was assumed to be the background therapy available to all patients in the model (irrespective of comparator arm).	The committee in TA935 preferred the assumption of the concomitant medication used from the manufacturer's clinical trial. The same principle was used here.

	Description of base case assumption	Justification
Health-state resource use	Resource use estimates for each health state were obtained from a physician survey, adjusted for severity in BE HEARD I and II and extrapolated using parametric modelling to derive estimates for the Very high response health state.	Using in the analysis the physician survey for resource use estimates from previous appraisals TA392 and TA935 [42, 44]. The extrapolation of the resource use for HiSCR90 was necessary to populate the health state value and differentiate the benefits of reduced resource use of Very high response.

Source: BE HEARD I and II [113, 114]
Abbreviations: AE, adverse event ; BKZ, bimekizumab; BSC, best supportive care; GLM, generalised linear model ; HS, hidradenitis suppurativa; HRQL, Health-Related Quality of Life; NMA, network meta-analysis; Q4W, every 4 weeks; RR, relative risk; SEC, secukinumab; TA, technology appraisal; UK, United Kingdom.

B.3.9 Base-case results

B.3.9.1 Base-case incremental cost-effectiveness analysis results

The base-case results are presented in Table 70, Table 71 and Table 72.

At the confidential PAS price, the ICER for bimekizumab was estimated below the £20,000 per QALY threshold against both comparators. Secukinumab was extendedly dominated by bimekizumab.

The additional health gains (QALYs) were 0.26 and 0.36 in the comparison with BSC and secukinumab, respectively.

Table 70 Fully incremental cost-utility base-case results

	Total		Incremental (vs reference)		ICER vs reference (BSC): £/QALY
	Cost (£)	QALY	Cost (£)	QALY	
BSC	[redacted]	[redacted]			
SEC	[redacted]	[redacted]	[redacted]	[redacted]	£27,143.94 (extendedly dominated by BKZ)
BKZ	[redacted]	[redacted]	[redacted]	[redacted]	£12,298.59

Abbreviations: BKZ, bimekizumab; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab.

Table 71 Pairwise comparisons base-case results

	Total		Incremental (vs BKZ)		ICER vs BKZ: £/QALY
	Cost (£)	QALY	Cost (£)	QALY	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,298.59
SEC	[redacted]	[redacted]	[redacted]	[redacted]	£1,832.32
BKZ	[redacted]	[redacted]			-

Abbreviations: BKZ, bimekizumab; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab.

Table 72 Incremental net health benefit

	Total		Incremental (vs BKZ)		NHB (vs BKZ)	
	Costs (£)	QALY	Costs (£)	QALY	At WTP £20,000	At WTP £30,000
BSC	[redacted]	[redacted]	[redacted]	[redacted]	0.26	0.40
SEC	[redacted]	[redacted]	[redacted]	[redacted]	0.36	0.37
BKZ	[redacted]	[redacted]			-	-

Abbreviations: BKZ, bimekizumab; BSC, best supportive care; QALYs, quality-adjusted life years; NHB, net health benefit; SEC, secukinumab; WTP, willingness-to-pay.

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis (PSA) (1,000 samples) are presented in Table 73, Table 74. One thousand samples were appropriate given a convergence test in the ICER values (Figure 32).

The total cost and QALY values were similar to those generated in the base case analysis. The values of the deterministic ICER and the average ICER of the 1,000 probabilistic samples differed due to the changes in the incremental QALYs.

Despite the differences in the ICERs, the direction of the results remains the same with the base case.

The probabilistic analysis estimated the ICER for bimekizumab below the £20,000 per QALY threshold against both comparators. Secukinumab was extendedly dominated by bimekizumab. The probability of cost-effectiveness at a WTP threshold of £30,000 was estimated over 70%.

Table 73 Fully incremental cost-utility probabilistic sensitivity analysis

	Total		Incremental (vs reference)		ICER vs reference (BSC): £/QALY
	Cost (£)	QALY	Cost (£)	QALY	
BSC	[redacted]	[redacted]			
SEC	[redacted]	[redacted]	[redacted]	[redacted]	£38,680.45 (extendedly dominated by BKZ)
BKZ	[redacted]	[redacted]	[redacted]	[redacted]	£18,823.34

Abbreviations: BKZ, bimekizumab; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab.

Table 74 Pairwise comparisons probabilistic sensitivity analysis

	Total		Incremental (vs BKZ)		ICER vs BKZ: £/QALY
	Cost (£)	QALY	Cost (£)	QALY	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£18,823.34
SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,062.36
BKZ	[redacted]	[redacted]	-	-	-

Abbreviations: BKZ, bimekizumab; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab.

Figure 32 Convergence plot (confidential)

Abbreviations: BSC, best supportive care; SEC, secukinumab.

The cost-effectiveness plane scatterplot and cost-effectiveness acceptability curve are in Figure 33 and Figure 34, respectively.

Figure 33 Cost-effectiveness plane scatterplot (confidential)

Abbreviations: Q4W, once every four weeks; QALY, quality- adjusted life years; WTP, willingness-to-pay.

Figure 34 Cost-effectiveness acceptability curve (confidential)

Abbreviations: Q2W, once every two weeks; Q4W, once every four weeks; QALY, quality-adjusted life years; WTP, willingness-to-pay.

B.3.10.2 Deterministic sensitivity analysis

The ten most influential variables in the deterministic sensitivity analysis (DSA) for the analysis of bimekizumab versus secukinumab and BSC are presented as tornado plots in Figure 35 and Figure 36 respectively. The Tornado plots show the change in the ICER from the deterministic base case when both the upper bound (shown in light green) and lower bound (shown in dark green) are applied.

The time horizon change assumed 10 years instead of the patient lifetime analysis in the base case. The change in the time horizon increased the ICER by £17,164.14 per QALY in the comparison with secukinumab and £33,047.97 in the comparison with BSC.

Relatively small changes to the result were observed when varying the RR for HiSCR50 of BSC vs. bimekizumab when conducting a pairwise comparison of bimekizumab versus secukinumab: £5,417.49 to -£10,209.20 at the lower and upper bounds respectively. The change to the ICER was more pronounced when bimekizumab was compared with BSC with the variation of the RR for HiSCR50 of BSC vs. bimekizumab yielding ICER changes of £7,802.67 to -£14,956.27 at the lower and upper bounds respectively.

Additionally, variation of the utility value post 16 weeks for the non-response state of patients receiving BSC treatment yielded an ICER change of -£3,627.04 at the lower bound and £21,551.09 at the upper bound. This is because extreme values were tested in this scenario: the low limit of the utility from the observed BE HEARD placebo data (16 weeks) and the high limit of the observed bimekizumab maintenance data (16-48 weeks).

In all DSA scenarios the ICER was retained below the £30,000 per QALY threshold when secukinumab is the reference treatment. In the comparison with BSC the limited time horizon (10 years) and the upper bound utility value for non-response with BSC increased the ICER beyond £30,000 per QALY. All other analyses were below the £30,000 per QALY threshold.

Figure 35 Tornado plot (BKZ versus SEC; confidential)

Abbreviations: BKZ, bimekizumab; BSC, best supportive care; HiSCR, hidradenitis suppurativa clinical response; ICER: incremental cost-effectiveness ratio; Q2W, once every two weeks; Q4W, once every four weeks; RR, relative risk; SEC, secukinumab.

Figure 36 Tornado plot (BKZ versus BSC; confidential)

Abbreviations: BKZ, bimekizumab; BSC, best supportive care; HiSCR, hidradenitis suppurativa clinical response; ICER: incremental cost-effectiveness ratio; Q2W, once every two weeks; Q4W, once every four weeks; RR, relative risk.

B.3.10.3 Scenario analysis

Scenario analyses tested the impact of certain assumptions and alternative inputs to the model result. Each scenario is described in Table 75. The input for scenarios 4 and 8 is outlined in Appendix M. The results of all the scenario analyses are presented in Table 76.

The ICER in the comparison with BSC ranged from £8,000 (scenario 12) to £93,000 per QALY (scenario 7). Compared with secukinumab, the results changed from bimekizumab dominating (10) to an ICER of £48,000 per QALY (7).

The change in the assumptions around the response levels after 16 weeks (2 to 7) produced the most pronounced differences in the ICERs across all scenarios: from £12,000 to £93,000 per QALY in the comparison bimekizumab vs. BSC and from £1,700 to £48,000 per QALY in the comparison bimekizumab vs. secukinumab. Some of this uncertainty is driven by the assumptions in the long-term efficacy of patients on BSC.

The base case analysis used a balanced approach for the long-term efficacy on BSC, while the alternative scenarios presented here included extreme assumptions that tested the plausibility of the model estimates. In scenarios 3 and 7 the BSC response was informed by the NMA-derived RRs for placebo vs bimekizumab, from the week 12/16 data observed in BE HEARD I and II. This produced improving response estimates for patients on BSC in the long-term, something that was contested by clinical experts. In scenarios 5 and 6, a gradual deterioration and a loss of response were assumed. Although these scenarios do not assume an improvement, they represent a counterintuitive assumption in suggesting that patients would continue treatment in the long term without a response benefit. Overall, the sensitivity analysis confirmed that despite the uncertainty around the long-term response of

patients on comparator treatment, the approach used in the base case, also used in previous TAs, represented the most balanced set of assumptions.

The inclusion of AEs (scenario 8) had a minimal change to the results.

Table 75 Outline of scenario analysis

#	Assumption or input	Description of scenario	Base case value	Rationale
1	Model structure / health states	Remove the Very-high response (HiSCR90) health state.	Separate High response (HiSCR75) and Very-high response (HiSCR90) categories.	Use the same model structure as in TA935 [44] (5 health states).
2	BSC response weeks 16-48	Loss of response: whereas 90.39% of the cohort would remain in their current state and 9.61% would move to the non-response state [172]. The probability of losing response (9.61%) was derived from an analysis of 36 weeks placebo arm data in PIONEER II [46].	A gradual deterioration of response. Under this assumption, patients cannot improve from their current state to a higher HiSCR response level.	This scenario reflects the committee's preferred base case for TA935.
3	BSC response weeks 16-48	Data from the NMA: the BSC response was informed by applying the NMA-derived RR for placebo vs bimekizumab, from the week 12/16 NMA results to the week 16-48 bimekizumab transition probability matrices		This scenario uses the same source for the effectiveness of BSC as for secukinumab.
4	SEC response long-term (48+)	Use the RR of secukinumab vs bimekizumab from the MAIC analysis (Appendix M for details).	The estimated RR from the NMA (at week 12/16) was applied to the bimekizumab transition probabilities to derive the transition matrix for secukinumab.	For reference, the respective estimates of RR of secukinumab vs bimekizumab, using a standard binomial model and the MAIC analysis are presented in Table 164
5	Durability of response with BSC	Gradual deterioration: using data from the placebo arm of BE HEARD (0–16-weeks).	Stable response in the long-term with BSC (adopting the TA392 approach).	Alternative assumption on BSC long-term response levels.
6	Durability of response with BSC	Loss of response; whereas 90.39% of the cohort would remain in their current state and 9.61% would move to the non-response state [172]. The probability of losing response (9.61%) was derived from an analysis of placebo arm data in PIONEER II [46]		
7	Durability of response with BSC	Use data from the NMA (data at 16 weeks); whereas the transition probabilities on BSC are informed by applying the RR of placebo vs bimekizumab from the NMA to the bimekizumab baseline transition probabilities for the period 16-48 weeks.		

#	Assumption or input	Description of scenario	Base case value	Rationale
8	Include AEs	See details in Appendix M.	No AEs included.	Consider the impact of AEs in the model results.
9	Mortality risk	Increase the mortality risk to patients in “Non-response” or “Partial response” health states.	Increased mortality risk for patients in the non-response health state (<HiSCR25)	Consider the impact of disease-mortality on patients with response below HiSCR50.
10	Mortality risk	General population mortality for all patients.		Remove any disease-specific mortality risk
11	Biologic use on BSC (effect on HRQoL and costs)	No utility benefit from using adalimumab during BSC. All patients gain the utility benefit observed in the BE-HEARD clinical trial for the placebo group (0-16 weeks data). BSC cost = 0	For 20.8% of the cohort (patients receiving biologic treatment), the model applied the maintenance BKZ (Q2W) observed values from BE HEARD I and II and added the cost of adalimumab biosimilar	Assess the impact of the treatment-related utility and adalimumab costs because of use of a biologic, despite non response.
12	HSUVs	Use utility values reported in NICE TA392	Treatment specific utilities derived from an analysis of EQ-5D data from BE HEARD I and II.	Assess the impact of different sources for patient utility in the model.
13	Very-high response resource use	Use the same resource use as for high response	An extrapolation was used to populate the Very-high response health state resource use.	Consider the same resource use levels as in previous TAs with 4 response categories.

Abbreviations: AE, adverse event; BSC, best supportive care; HiSCR, hidradenitis suppurative; HRQoL, health-related quality of life; HSUV, health state utility values; NICE, National Institute for health and Care Excellence; SEC, secukinumab; TA, technology appraisal.

Table 76 Scenario analyses results (deterministic)

#	Treatment	Total		Incremental (BKZ – Comparator)		ICER (£/QALY)
		Costs (£)	QALYs	Costs (£)	QALYs	
Base case	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,298.59
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£1,832.32
	BKZ	[redacted]	[redacted]			
1	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,434.15
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£1,929.41
	BKZ	[redacted]	[redacted]			
2	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£21,594.42
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£7,776.03
	BKZ	[redacted]	[redacted]			

#	Treatment	Total		Incremental (BKZ – Comparator)		ICER (£/QALY)
		Costs (£)	QALYs	Costs (£)	QALYs	
3	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£48,702.67
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£20,441.40
	BKZ	[redacted]	[redacted]			
4	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,298.59
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£1,691.29
	BKZ	[redacted]	[redacted]			
5	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£91,165.17
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£46,926.52
	BKZ	[redacted]	[redacted]			
6	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£85,949.25
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£42,891.08
	BKZ	[redacted]	[redacted]			
7	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£93,190.75
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£47,605.78
	BKZ	[redacted]	[redacted]			
8	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,281.26
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£1,817.10
	BKZ	[redacted]	[redacted]			
9	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,808.17
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£354.19
	BKZ	[redacted]	[redacted]			
10	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£11,971.11
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	BKZ dominates
	BKZ	[redacted]	[redacted]			
11	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,515.71
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,597.63
	BKZ	[redacted]	[redacted]			
12	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£7,778.38
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£1,139.44
	BKZ	[redacted]	[redacted]			
13	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,466.32
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£2,047.55
	BKZ	[redacted]	[redacted]			

Abbreviations: BKZ, bimekizumab; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SEC, secukinumab.

B.3.10.4 Summary of sensitivity analyses results

The analysis examined the cost-effectiveness of bimekizumab through PSA, DSA, and scenario analysis.

PSA showed consistent total costs and QALY values with the base case, with variations in ICERs not altering the conclusion that bimekizumab is cost-effective below the £20,000 per QALY threshold against both comparators. Secukinumab was extendedly dominated, and bimekizumab's cost-effectiveness probability was over 70% at a £30,000 willingness-to-pay (WTP) threshold.

Model value changes in DSA indicated that all ICERs remained below the £30,000 per QALY threshold except two occasions in the comparison with BSC: when the time horizon was limited to 10 years instead of lifetime and when the utility post 16 weeks on BSC was using an extreme high limit.

Further scenario analysis tested several of the model assumptions and its structure. The separation of High response levels (HiSCR75) to High and Very High (HiSCR90) had a small impact on the results. The long-term response of patients on comparator treatments (including BSC) introduced uncertainty. However, most of the scenarios were testing extreme assumptions that were considered implausible by clinical experts and produced counterintuitive estimates.

Overall, the sensitivity analysis across PSA, DSA, and scenario analysis underscores the robustness of the cost-effectiveness estimates of bimekizumab in treating HS compared to secukinumab and BSC under various assumptions and analysis settings.

B.3.11 Subgroup analysis

No subgroup analyses were conducted.

B.3.12 Benefits not captured in the QALY calculation

In addition to the utility gains associated with improvements in HiSCR responses, there may be further benefits in patient quality of life from treatment with bimekizumab that are not captured in the analysis.

The use of HiSCR to allocate quality of life gains has the following limitations. Firstly, HiSCR response does not comprehensively consider the impact of draining tunnels, which is an important factor for patient quality of life. Secondly, HiSCR represents a binary outcome (response yes/no) which may miss nuances of a continuous treatment effect—for instance, a person that has all draining tunnels resolved but gains one inflammatory nodule is a non-responder.

Other limitations of the HS trials include the inability to capture the positive effect that systemic treatment has on the success rates of surgery. Clinical advisers, including an NHS surgeon who specialises in HS, have stated that treatment allows patients to undergo surgeries they would not be able to have otherwise due to disease activity and inflammation. Successful surgery is expected to lead to less frequent future surgeries and higher quality of life after surgery, as shown in the SHARPS study [109]. However, there is little evidence at this moment to quantify the impact of these hypotheses in an economic model. Such

evidence will be possible to consider when real-world data capture the impact of bimekizumab in patients with HS.

Additionally, due to regulatory requirements, the clinical trials which informed the analysis were not designed to capture the expected benefits of concomitant treatment with antibiotics in HS. For example, the efficacy for bimekizumab was higher in a real-world evidence study where antibiotic use was allowed, than in the BE HEARD I and II trials [140].

Furthermore, HS is associated with comorbidities including axial spondyloarthritis and psoriatic arthritis [173-175], as well as with an elevated risk of psoriasis [176]. Bimekizumab is licensed and recommended by NICE for the treatment of all three of these conditions. Accordingly, the introduction of bimekizumab as a treatment for HS could have benefits for patients with these comorbidities. These potential benefits are not captured within the cost-per-QALY analysis included in this appraisal, which captures only benefits directly associated with the treatment of HS.

HS affects people of prime working age and is associated with high unemployment, slower income growth, and a higher risk of leaving the workforce [21]. Accordingly, bimekizumab has the potential to improve patients' professional lives, while reducing the cost of HS to society.

Out-of-pocket costs associated with wound care, which disproportionately affect Black people over White people and women over men [21], may be reduced by more effective treatment of HS; this is not captured in the economic model.

HS also affects patients' family members [81, 82]. This impact may be reduced by effective treatment, but is not included in the QALY calculation.

B.3.13 Validation

B.3.13.1 Validation of cost-effectiveness analysis

The economic model underwent review by an advisory board of practicing clinicians in England and health economists. Quality control, and external technical validation was conducted via a NICE PRIMA review in 2023.

Further quality-control for the verification of the input data and programming was performed by staff not involved in the model development and in accordance with a prespecified test plan. Programming validation included checks of the model results, calculations, data references, model interface, and Visual Basic for Applications code. The model calculations were also verified in 2024 by an independent agency.

B.3.13.2 Interpretation and conclusions of economic evidence

The cost-effectiveness of bimekizumab for patients with moderate-to-severe HS for whom adalimumab is contraindicated or otherwise unsuitable was evaluated compared to two relevant treatment strategies, secukinumab and BSC, available in UK clinical practice. The analysis perspective on cost was NHS and PSS.

The economic evaluation was based on the population of patients enrolled in two 48-week phase 3 RCTs, BE HEARD I and BE HEARD II. The trial population included patients with previous biologic exposure, particularly adalimumab and biologic-naïve patients. Subgroup analysis indicated that the efficacy was consistent between bio-naive and bio-experienced patients. Consequently, the trial ITT population was used as the most relevant source for the efficacy of bimekizumab.

Without direct evidence, the comparative effectiveness of secukinumab and BSC in the economic model was sourced from an NMA conducted on the response levels at week 12/16.

The model results reflected the comparative effectiveness observed in the clinical trials and estimated in the NMA, showing the bimekizumab model arm generating more QALYs than secukinumab or BSC.

Furthermore, the model used a framework similar to the one considered by NICE in previous TAs and captured the critical characteristics of HS and the clinical care pathway for the patient population addressed in the decision problem for this submission.

The long-term follow-up data from the BE HEARD trials demonstrated a sustained benefit for patients on bimekizumab. Nevertheless, extrapolation of the data was necessary to reflect on the patient's condition over a lifetime. This data limitation added to the model input uncertainty, and several scenarios were explored to demonstrate the differences in the results.

The base case deterministic and probabilistic total cost and utility estimates for all strategies were very similar, suggesting a high level of robustness of the results to the uncertainty in the analysis inputs. Most model iterations in the deterministic sensitivity results (one-way and scenarios) were close to the base case.

Overall, the base case deterministic and probabilistic analyses are closely aligned, and most iterations of the scenario analysis produced ICER values below £30,000 per QALY gained. The analysis suggests that bimekizumab will generate cost-effectively substantial health benefits for HS patients and should be a valuable investment for the NHS.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Bimekizumab for treating moderate to severe hidradenitis suppurativa [ID6134]

Summary of Information for Patients (SIP)

April 2024

File name	Version	Contains confidential information	Date
[ID6134] Bimekizumab HS SIP	1.0	No	24 April 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Generic name: Bimekizumab Brand name: Bimzelx®

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Adults with moderate to severe hidradenitis suppurativa (HS) for whom: 1. Conventional treatments, such as oral antibiotics, are not effective. 2. Adalimumab is unsuitable, including those for whom adalimumab has not worked or has stopped working.

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Bimekizumab is currently pending authorisation by the Medicines and Healthcare Products Regulatory Agency (MHRA; the regulatory body in the United Kingdom) for the treatment of HS.

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Not applicable.

Section 2: current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is the main disease that the medicine plans to treat?
HS is a debilitating, long-term skin disease that can result in intense pain. It causes recurrent boil-like lumps in certain areas of the body that become inflamed, and can lead to abscesses (sores), irreversible skin damage, tunnels under the skin (some of which will become tunnels that leak pus, commonly known as draining tunnels), and scarring [1-5]. HS mostly occurs in skin folds (areas where the skin overlaps) [1-3], with the most common areas of the body affected being the armpits and intimate areas such as the groin, buttocks, genitals and breasts [6]. HS can also affect the face, back and inner thighs [6].

In HS, the body's immune system, which usually acts to fight off infection and heal injury [7], attacks hair follicles, causing inflammation (redness, tenderness and swelling) [8, 9]. Two proteins in the body called interleukin-17A (IL-17A) and interleukin-17F (IL-17F) are involved in causing this inflammation.

How many people have HS and what age are patients typically diagnosed?
HS affects around 1 in 130 people (0.77%) in the United Kingdom, corresponding to approximately 435,000 people in England [10]. HS is typically diagnosed in young adults aged 20–40 years [11-13]. Around 45% of people with HS have moderate to severe disease [6].

What are the main symptoms of HS?
The symptoms of HS can be severe and debilitating, and include pain and discomfort, including pain when sitting, itching, skin damage, infection, foul-smelling discharge and restricted and painful movement of arms and legs. The pain experienced by people with HS can also affect the quality and duration of sleep and can cause insomnia [2, 6]. In addition, patients experience periodic worsening of symptoms, including pain, known as disease flares [14, 15].

What is the burden of HS and the impact on quality of life?
Results from a European study indicated that the impact of HS on quality of life is worse than that observed in many skin diseases, such as psoriasis, and is similar to or worse than that observed in patients with rheumatoid arthritis pain, chronic obstructive pulmonary disease, cancer and cardiovascular disease [16].

Patients with HS commonly experience extremely high levels of pain. In a global survey, recent HS-related pain was rated by patients on a numeric scale from 0 (no pain) to 10 (worst possible pain): most participants (61.4%) rated the pain as moderate or higher (≥ 5), and 4.5% described the pain as being the worst possible (10) [17].

The symptoms of HS severely affect patients' self-esteem and mental health [17-20]. Anxiety and depression are common amongst patients with HS and patients have also reported feeling extremely withdrawn and embarrassed due to their condition [17]. Additionally, sexual health is severely affected in patients with HS [18]. In a survey, nearly all women (94.3%) and most men (80.8%) said HS made it harder to have relationships or sexual relations [21, 22]. HS tends to affect women who are of childbearing age, which can significantly affect their plans for starting a family [23].

Given that people with HS are often young adults when diagnosed [11-13], HS can also severely impact education and professional lives. HS is associated with high unemployment, slow income growth and a high risk of leaving the workforce [22]. Additionally, during HS disease flares, patients often struggle to carry out simple day-to-day tasks and may have to take time off work [24].

Patients may routinely need dressings for pus-producing abscesses and draining tunnels [25, 26]. This can be time consuming, and issues around dressings can lead to patients avoiding going out in public for long periods of time, impacting their ability to work, exercise and contribute to society [24]. The most appropriate dressings are not routinely prescribed, leaving patients with significant out-of-pocket costs [22].

What is the impact on family members of patients with HS?
In addition to the effect of HS on patients, studies have found that this disease also reduces the quality of life of family members, particularly as a result of anxiety, depression and sexual dysfunction [21, 27].

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is HS diagnosed?
HS is diagnosed based on the type, location and frequency of any lesions [28, 29]. Delays in diagnosis and misdiagnosis are significant issues for patients with HS, with an average time from symptom onset to diagnosis of 10 years [17, 22, 30]. HS is often misdiagnosed as abscesses, boils and ingrown hairs, which can lead to inappropriate treatment for some patients [22]. As HS can develop during puberty, it can also sometimes be misdiagnosed as acne. Additionally, the areas of the body in which the disease typically presents means it can be misdiagnosed as a sexually transmitted infection [30, 31]. In a UCB survey of 59 patients with HS in the UK conducted in March 2024, 92% of respondents reported receiving at least one misdiagnosis prior to being diagnosed with HS [32]. Patients stated that [32]:

*"I'd gone through about **12 years** before I even had any kind of answers."*

*"Someone should have **diagnosed me sooner**, someone **should have noticed**… I shouldn't have spent **year on year with ineffective treatments as the disease progressed.** But I appreciate **I can't turn back time,** so this is what I now accept."*

Doctors commonly define HS disease severity using a measure called the Hurley scale [33-35], which comprises three stages: (I) single or multiple abscesses with no tunnels or scarring; (II) recurrent single or multiple widely separated abscesses with tunnels and scar formation; and (III) diffuse involvement OR multiple interconnecting abscesses and tunnels.

Why does speed of diagnosis matter?
The longer the delay until diagnosis, the greater the disease severity at diagnosis. Diagnostic delays can lead to poor health outcomes [22, 36]. In particular, treatment is most likely to be effective if started in a disease stage with reversible lesions (i.e. lesions that can be healed) such as inflammatory nodules and abscesses, rather than after the development of irreversible lesions such as complex draining tunnels and scarring [36].

Misdiagnosis can also lead to frustration and can create a difficult relationship between a patient and their doctor [22]. Some patients choose not to seek further help due to negative experiences [22].

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:

    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.

    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Current treatments

Conventional treatment

Based on guidance issued by the British Association of Dermatologists [25] and the Primary Care Dermatology Society [26], initial treatment of HS may consist of antiseptic and antibiotic medications applied to the skin. If relevant, weight loss and smoking cessation advice may also be offered alongside initial disease management [25, 37]. If initial treatment is unsuccessful the use of antibiotics taken orally is recommended [25, 26]. Retinoids such as acitretin or the anti-inflammatory antibiotic, dapsone, may be considered when earlier treatments have not worked [25].

For patients for whom conventional treatment is ineffective, the next step is surgery or biological therapy [25].

Biological therapies

Biological medicines are made from proteins or other substances produced by the body. For patients with moderate to severe HS which has responded inadequately to conventional treatment, adalimumab (which reduces the activity of a protein called tumor necrosis factor) is recommended [25, 38].
Secukinumab (which reduces the activity of IL-17A) is an option for treating active moderate to severe HS in adults when it has not responded well enough to conventional treatment, only if adalimumab is not suitable, did not work or has stopped working [39].

Surgery

Surgical treatment is also a potential option for patients with HS [40]. Surgical approaches include the following [29]:

- Incision and drainage, where the surgeon cuts into an abscess and pus is drained.
- Deroofing, a procedure in which the “roof” (i.e. top skin layer) of an abscess or tunnel is removed.
- Local excision (i.e. removal) of the lesion and direct closure of the surgical wound.

- Wider excision of the lesion and surrounding area [37].

In clinical practice, surgery and adalimumab may be used together, and there is evidence that this may be more effective than surgery alone [41]. There is evidence that when biological treatments are started a short time after surgery, this can also reduce the risk of disease recurring at the site that was operated on [42].

Limitations of current treatments for HS

For both adalimumab and secukinumab, about half of patients do not have a clinical response to initial treatment [43, 44], and for some patients treatment works at first and then stops working (secondary failure) [39, 45].

A global survey study found that around 46% of people with moderate to severe HS were not satisfied with their current treatment [17]. The main reasons for dissatisfaction were poor efficacy (42%) and side effects after taking treatment (adverse events; 19%) [17].

In the UCB UK patient survey, only a minority of participants believed their current HS treatment provided full relief for their symptoms (mild HS, 47%; moderate HS, 34%; severe HS, 20%) [32].

Although surgery is effective in removing lesions, HS may recur after an operation. For example, in studies in France and the USA, 35% and 41% of surgical procedures were followed by a lesion occurring again at the same site [46, 47].

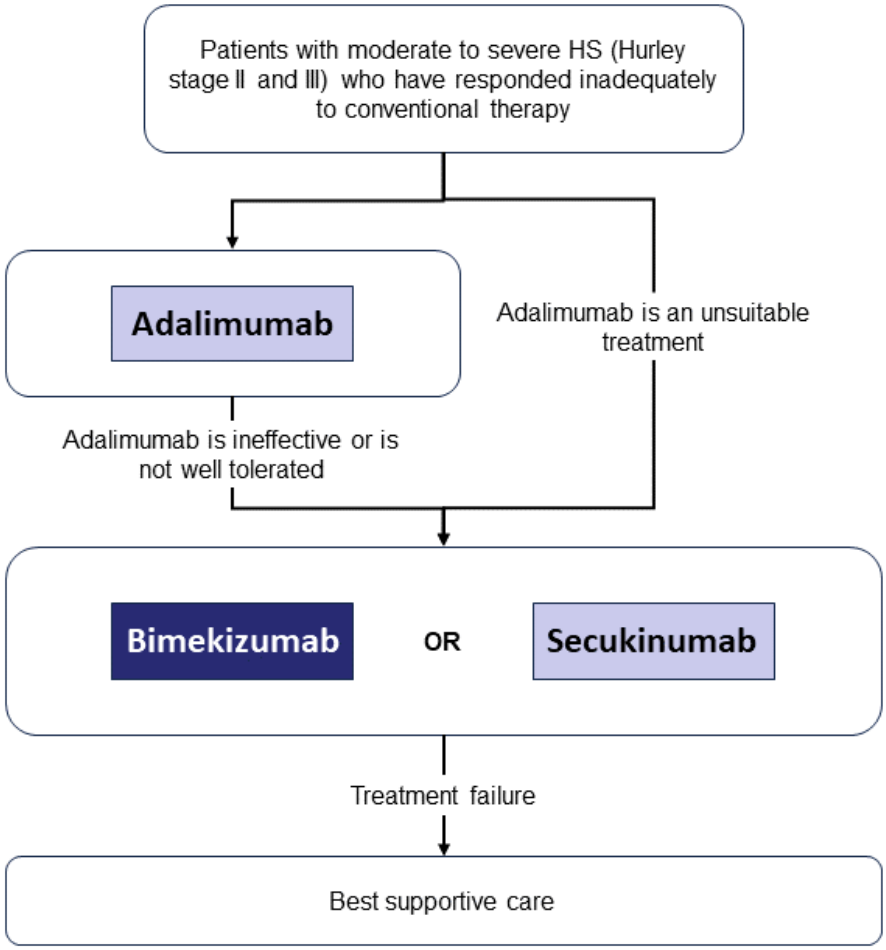
Accordingly, for patients with moderate to severe HS there remains a need for additional safe and effective therapies.

Bimekizumab

Bimekizumab works by targeting two proteins in the body called IL-17A and IL-17F, which are involved in causing inflammation in HS. In human cells, inhibiting (i.e. blocking and reducing the effect of) both IL-17A and IL-17F with bimekizumab reduced inflammation to a greater degree than inhibiting IL-17A alone [48].

As shown in Figure 1, bimekizumab is proposed for adult patients with moderate to severe HS who have an inadequate response to conventional treatments and for whom adalimumab is unsuitable, including those for whom adalimumab has not been effective or has stopped being effective.

Figure 1. Anticipated treatment pathway for patients with moderate to severe HS which has responded inadequately to conventional systemic therapy, including proposed positioning of bimekizumab.



HS, hidradenitis suppurativa.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

In January 2024, UCB ran a focus group, a session where eight UK patients with HS could share their experiences of living with the disease [23]. Building on themes identified during the focus group, UCB, in collaboration with clinicians, developed a patient survey which was conducted in March and April 2024, with a total of 59 patient responses [32, 49].

Key themes are summarised below.

HS has a negative impact on almost every aspect of patients' lives [32]:
*"…try and think about what it doesn't affect, and I can't think of anything it doesn't affect. It affects my **mobility**, **mental health**, **self-esteem**, **self-worth**, the **clothing I wear**, my **social plans**, my **sex life**, my broader **relationships** as a **daughter**, a **sister**, a **friend** or **colleague**, my **ability to start a family**, the **chance to reach the level I wanted to in my career**, **physical activity**, my **employment** through being absent or not as productive, it has costs attached in terms of time off work for **sickness**, **surgery**, **appointments**, **travel** and **parking costs**, **buying OTC pain relief**, **dressings**, **additional clothes**, **laundry**."*

Overall, HS has a substantial impact on education, work, and relationships. Patients emphasised feelings of intense pain, social isolation, embarrassment and severely impacted mental health.

Pain

*"You can't sleep – **if you as much as twitch, it's like being stabbed**. Until it starts to drain, and that could be a week, that's a week in agony."*

*"Even talking when it's flared on my face is **complete agony**."*

Pain has a significant effect on people's ability to live "normal" lives, affecting their physical and emotional wellbeing and impacting relationships and work. In the UCB survey, 80% of participants had experienced pain in the last 6 months, and 98% said that pain was the top symptom that they most wished would disappear [32]. Among patients experiencing pain in the last 6 months [32]:

- 71% agreed that 'no one understands the intensity of the pain …'
- 64% agreed that 'no one understands how much pain I experience …'
- 78% agreed that 'the pain makes me irritable.'
- 74% agreed that 'the pain has a negative impact on my social life.'
- 63% agreed that 'the pain has a negative impact on my mental health.'
- 64% agreed that they were 'not able to enjoy my life because of … pain.'
- 51% agreed that 'the pain has a negative impact on my professional life.'

*"It is **difficult for others to truly understand the pain** and the limitations caused by HS, in part because people can't see it. Sometimes what doesn't look like much is **10 out of 10 in pain**, and other times, something which can look terrible, can be far less painful."*

*"So I **haven't been able to work for a while now because of the pain**. It was like a **domino effect** – I was in pain, then the fatigue and then I was **flaring more***

*because I was stressed. Not being able to go to work because I was **covered in flares**, and I was in pain – it was having just a **huge effect on everything.**"*

Education and professional lives
HS can often develop during teenage years and puberty negatively impacting people's education – over a third of survey respondents (37%) told us that HS had a big to devastating impact on their ability to participate in education, and a quarter (27%) that HS had a big to devastating impact on their ability to hold down a job [32].

*"I think when you are younger and potentially don't have a diagnosis or newly diagnosed, **it's harder, earlier in life to advocate for yourself** and confidently ask for reasonable adjustments at school/college/university and then in the workplace."*

*"HS **put an end to my PhD and research career** and a promised lecturing faculty position."*

*"I'm 30. I've never worked, I've never had a job. **At every point HS has interrupted my life."***

*"**I haven't been able to work for 3 or 4 years now** because of the pain."*

Impact on relationships, intimacy and starting a family
Some patients emphasised the impact that HS had on their relationships and plans to start a family [23].

*"Just the other **day I saw a friend from high school, and she'd had a baby, and it hit hard…**I love (my family) dearly. But just looking at them, it hurts so much because I've not been able to achieve that. It hurts. Left behind is the exact term I would use."*

One patient shared that they feared HS was hereditary and they would not want to inflict the disease on a child.

Fatigue
51% of survey respondents reported regularly or constantly experiencing fatigue and/or lack of sleep [32].

***"**I think one of the physical things I found, that **nobody talked about** when I was first diagnosed back in the late 90s, is the **fatigue**, the **inflammation in the rest of my body**, my joints and muscles. That sense of just thinking, '**I can't be this tired, I haven't done anything!'**. And then you're not able to do **normal things**, so you **can't be yourself**."**

Physical activity
53% of survey respondents said that HS had a considerable to devastating impact on their ability to exercise or stay active [49].

*"HCPs **don't seem to get that I was once a healthy person** who did lots of exercise, and now I can't do it. So, when somebody says, 'have you thought of doing some exercise?', **I want to slap them!"***

"I started as within healthy range of weight for my height and age before this started and am incredibly active, that has all changed since this disease invaded my body."

Guilt & stigmatisation

26% of survey respondents said they regularly or constantly experienced guilt as a result of HS, and 42% said they regularly or constantly felt stigmatized as a result of their HS [32].

Social isolation

*"They just saw me as unreliable. They **stopped including me in social situations** as they knew I might not show up or drop out at the last minute."*

*"It's the pain, it's the leakage, it's embarrassing. Going out for a meal, getting up from the seat and seeing there's something there that wasn't there before you sat down – **it's soul-destroying – absolutely awful**."*

Mental health, depression, anxiety, self-harm, and suicide

*"A really acute flare can still just get me and take me to the lowest possible place, and I think the amount of people, myself included, who have done that and said **I'd rather not be here anymore than live with this relentless pain**."*

*"I think **body dysmorphic symptoms** go hand in hand with this condition…"*

These themes are also reflected in other, larger studies:

- A survey in the EU5 (France, Germany, Italy, Spain, and the UK) and the USA described the areas most affected by HS as being personal appearance and self-confidence (proportion greatly affected: 15.1%), mood (12.7%), close personal relationships (10.2%), feelings about the future (6.8%), leisure activities (6.8%), and motivation (6.5%) [6].
- In a Danish survey of patients with HS, a substantial proportion reported limitations in daily life, including problems with mobility (32% of patients), self-care (16%), usual activity (45%), pain/discomfort (79%), and anxiety/depression (40%) [50].
- In the UNITE study (an international survey of patients with active HS from Australia, Canada, Europe and the USA), patients were especially affected (rated as 'a lot' or 'very much') by skin-related symptoms of the disease including pain (59.2%), how the disease influenced the clothes they wore (56.3%), and the embarrassment and self-consciousness experienced (53.5%) [20].
- In a study conducted in Greece, patients with HS were found to have higher anxiety, depression, and loneliness and social isolation scores, and lower self-esteem scores, than healthy individuals [51].

Patients in the focus group also highlighted that treatments sometimes stop working and that there is a need for additional treatments and support from their doctors [23]:

*"I'm hopeful because of my dermatologist now, that **she will endeavour to seek out something that will work for me, and if that stops, something else**."*

*"I have tried everything I can as a female at my age and have been **waiting for the next new biologic**…"*

To summarise: this evidence demonstrates the substantial burden that HS has on the lives of patients, and the need for additional treatments.

Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body.

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

About bimekizumab – its key features and how it works
Bimekizumab is a medicine that has already been approved by the MHRA for treating the following inflammatory diseases:

- plaque psoriasis (a skin condition with symptoms including pain, itching and scaling of the skin).
- psoriatic arthritis (a disease that causes inflamed joints, often accompanied by plaque psoriasis).
- axial spondyloarthritis (a disease primarily affecting the spine which causes inflammation of the spinal joints).

Bimekizumab is a type of biological therapy known as a monoclonal antibody. It binds with high affinity to two key inflammatory proteins in the body called IL-17A and IL-17F, preventing them from promoting inflammation.

Innovation in patient care
Current biological therapies for HS inhibit either IL-17A (but not IL-17F), or another protein called tumor necrosis factor. For a substantial proportion of patients, these therapies are not effective or stop working after a period of time. Bimekizumab is an innovative, alternative treatment option that inhibits IL-17F in addition to IL-17A. By reducing the activity of both of these key inflammatory proteins, bimekizumab can reduce inflammation and improve disease symptoms and patient quality of life.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

No.

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Not applicable.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Bimekizumab is given by injection under the skin (subcutaneous injection) at a dose of 320 mg once every 2 weeks for a period of 16 weeks (initial therapy). After the initial 16-week treatment period, bimekizumab is given at a dose of 320 mg every 4 weeks (maintenance therapy).

The patient and their doctor or nurse will decide if the patient should inject bimekizumab themselves. Bimekizumab should not be injected unless the person giving the injection has been trained by a healthcare professional.

Adalimumab and secukinumab are also given by subcutaneous injection, but at different frequencies:

- adalimumab – every 2 weeks for the first 4 weeks, then weekly or every 2 weeks.
- secukinumab – weekly for first 4 weeks, then monthly. Some patients may use secukinumab every 2 weeks instead of monthly; however, guidance on when this should be considered is unclear [39].

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location,

population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The following table presents four clinical trials to date assessing bimekizumab in HS. One trial is ongoing and three have been completed [52-62].

Study name (ClinicalTrials.gov ID)	Phase	Location	Patient group	Number of patients	Treatments studied	Expected completion date
HS0001 (NCT03248531) [63]	2	International	Adult patients with moderate to severe HS	90	Bimekizumab, adalimumab, placebo	Completed
BE HEARD I (NCT04242446) [64]	3	International	Adult patients with moderate to severe HS	505	Bimekizumab, placebo	Completed
BE HEARD II (NCT04242498) [65]	3	International	Adult patients with moderate to severe HS	509	Bimekizumab, placebo	Completed
BE HEARD EXT (NCT04901195) [66]	3	International	Participants in BE HEARD I or II who completed the maintenance treatment period through Week 48, were eligible to receive bimekizumab at the time of completing the feeder study and did not meet any withdrawal criteria of the feeder study.	658	Bimekizumab	July 2026

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The efficacy and safety of bimekizumab in the treatment of moderate to severe HS has been investigated in two 48-week clinical trials, BE HEARD I and BE HEARD II.

The trials included adult patients (aged at least 18 years) with a diagnosis of moderate to severe HS for at least 6 months and a history of inadequate response to systemic antibiotics (i.e., antibiotics that treat the whole body) for treating HS. Treatment groups in the trials were as follows:

- Bimekizumab 320 mg every 2 weeks throughout (Q2W)
- Bimekizumab 320 mg every 4 weeks throughout (Q4W)
- Bimekizumab 320 mg every 2 weeks for the first 16 weeks, then every 4 weeks (Q2W/Q4W) for the remaining 32 weeks
- Placebo (a substance containing no active drug) for the first 16 weeks, then bimekizumab 320 mg every 2 weeks for the remaining 32 weeks

In the original analysis that was designed before the trial data became available, if a patient took a systemic antibiotic for any reason they were labelled as having no response or missing (depending on what was being measured) after taking that antibiotic. However, many patients in the trials received systemic antibiotics for reasons other than to treat HS. Therefore, the original analysis may not accurately capture the clinical benefit of the drug.

To account for this, a *post hoc* analysis (i.e., an analysis that was designed after the trial data became available) was conducted. In this *post hoc* analysis, only patients who received a systemic antibiotic specifically for treating HS (but not other conditions), were labelled as having no response or as missing after taking the antibiotic, depending on what was being measured. Patients were also labelled as having no response/missing if they stopped taking treatment because it was not working or because they experienced an adverse event. BE HEARD trial data presented in this section are from a *post hoc* analysis.

The primary endpoint (the main outcome of interest) in both trials was HiSCR50 (“HiSCR” stands for hidradenitis suppurativa clinical response) at week 16. HiSCR50 is defined as the proportion of patients having a ≥ 50% reduction from baseline (i.e., from the start of the trial) in total abscess and inflammatory nodule count, with no increase from baseline in abscess or draining tunnel count. HiSCR50 is often used in clinical trials to measure the efficacy of biologics, compared with placebo, for the treatment of HS [43, 67, 68].

In both trials, the proportion of patients achieving HiSCR50 was higher in the group receiving bimekizumab Q2W than in the placebo group (BE HEARD I: bimekizumab 320 mg Q2W, 55.2%; placebo, 34.0%; BE HEARD II: bimekizumab 320 mg Q2W, 58.7%; placebo, 32.3%). Patients were also more likely to achieve HiSCR75, HiSCR90 and HiSCR100 responses (75%, 90% and 100% reductions from baseline in total abscess and inflammatory nodule count, with no increase from baseline in abscess or draining tunnel count) with bimekizumab Q2W than with placebo at week 16. This shows that the greater efficacy of bimekizumab over placebo continues even when higher thresholds for the reduction in total abscesses and inflammatory nodules are used. Additionally, the majority of

patients who received bimekizumab 320 mg Q2W and achieved a HiSCR50 response also achieved a HiSCR75 response or greater at week 16.

Most patients initially treated with bimekizumab Q2W retained their week 16 HiSCR responses during 32 weeks of subsequent bimekizumab 320 mg Q4W treatment; 88.5% of patients maintained their HiSCR50 responses and 88.3% of patients maintained their HiSCR75 responses. It was considered unethical to treat patients with placebo for longer than 16 weeks. Therefore, it is not possible to compare bimekizumab to placebo using data after week 16.

After 48 weeks of treatment with bimekizumab:

- Patients with a HiSCR90 response (meaning they achieved a substantial clinical improvement) at the end of the initial 48 weeks were given bimekizumab 320 mg every 4 weeks (Q4W) for an additional 48 weeks.
- Patients without a HiSCR90 response continued with a higher dose of bimekizumab, receiving 320 mg every 2 weeks (Q2W) during the subsequent 48-week period.

At 96 weeks, approximately two-thirds of patients who received bimekizumab 320 mg Q2W/Q4W/Q4W (which involves initial treatment with bimekizumab Q2W for 16 weeks, followed by bimekizumab 320 mg Q4W for 32 weeks, and then bimekizumab 320 mg Q4W for another 48 weeks) achieved a HiSCR100 response (the most stringent HiSCR measure).

A limitation of HiSCR measures is the lack of dynamic measurement of draining tunnels, meaning that the effect of treatment may not be fully captured [69]. In principle, patients could achieve HiSCR100 but still have active draining tunnels [62] which could cause significant pain and chronic discharge [2, 69, 70]. To address this issue, the BE HEARD trials also used the International HS Severity Score System (IHS4). The IHS4 score is calculated as 1 x the number of nodules plus 2 x the number of abscesses plus 4 x the number of draining tunnels. An IHS4 score of 3 points or fewer is categorised as “mild” disease.

Bimekizumab, administered at a dose of 320 mg every two weeks (Q2W) or 320 mg every four weeks (Q4W), demonstrated significant effects on disease severity over a 96-week period, as assessed by the IHS4. Approximately three-fifths of patients receiving bimekizumab 320 mg Q2W/Q4W/Q4W were categorised as having mild HS at the end of 96 weeks. For patients on bimekizumab 320 mg Q2W/Q4W/Q2W, just over a third were in the mild category at the same time point.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Pain
Patients rated their worst skin pain on an 11-point numerical scale every day, with a higher value corresponding to more severe pain. The data were analysed as weekly averages. Patients treated with bimekizumab 320 mg Q2W had larger mean improvements in worst daily skin pain at week 16 than those receiving placebo (BE HEARD I: −1.98 vs −0.92, respectively; BE HEARD II: −1.87 vs −0.45, respectively).

A further definition of skin pain response, a Hidradenitis Suppurativa Symptom Questionnaire (HSSQ) score of 0 – indicating no skin pain – among patients with baseline scores ≥ 1, also showed higher response rates for bimekizumab Q2W than for placebo at week 16 (bimekizumab 320 mg Q2W: 7.1−10.8%, placebo: 2.3%). The proportion of patients with HSSQ 0 increased from week 16 to week 48 in all bimekizumab groups [71].

Health-related quality of life
Health-related quality of life (HRQoL) is an assessment of the impact of illness and treatment on a patient's sense of overall function and wellbeing [72]. In the BE HEARD trials, HRQoL was assessed using the Dermatology Life Quality Index (DLQI) and the Hidradenitis Suppurativa Quality of Life (HiSQOL) questionnaire. The DLQI comprises ten questions based on skin disease symptoms and impact on HRQoL [73]. Scores range from 0 to 30, with higher scores indicating worse HRQoL [73]. A 4-point improvement is defined as a clinically meaningful change among patients with baseline scores of at least 4 [74]. The HiSQOL is a 17-item HS-specific questionnaire with three subscales: symptoms, psychosocial, and activities and adaptations [75].

Treatment with bimekizumab 320 mg Q2W was associated with improvements in HRQoL, with 56.5% of patients with a baseline DLQI of at least 4 having a clinically meaningful improvement after 16 weeks (compared with 45.9% taking placebo). At 48 weeks, 51.4% patients taking bimekizumab 320 mg Q2W/Q4W had a clinically meaningful response, as measured using the DLQI. Substantial improvements in HiSQOL scores were also observed at 16 weeks and 48 weeks for patients taking bimekizumab.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The safety data collected from the BE HEARD trials were generally consistent with safety results collected from other trials assessing bimekizumab for different diseases [76-80], and no new safety issues were identified.

An increased incidence of oral candidiasis (a fungal infection that affects the mouth and throat) was seen for patients who took bimekizumab compared with those who took placebo (initial treatment period: bimekizumab 320 mg Q2W, 7.1%; placebo, 0%). However, most cases were mild to moderate, able to be resolved with appropriate antifungal therapy, and did not lead to patients stopping bimekizumab treatment.

Across the bimekizumab HS clinical trial programme, one patient with significant cardiovascular history died of congestive heart failure, which was considered unrelated to bimekizumab treatment by the study investigator (BE HEARD I: bimekizumab 320 mg Q2W/Q2W group).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

There are limited effective options for treating HS, especially in people for whom adalimumab does not work or is not well tolerated (i.e., may have increased side effects). Current biologic drug options for HS often also only work for a limited period of time [39, 43, 45, 81, 82]. Results from the BE HEARD trials show that bimekizumab offers an effective, tolerable, and potentially long-term treatment option for people with moderate to severe HS.

The way in which bimekizumab works is different to adalimumab and secukinumab, so people for whom adalimumab or secukinumab does not work or is not well tolerated may respond to treatment with bimekizumab.

After proper training, people with HS can potentially self-inject bimekizumab themselves. This means that they may be able to have their treatment at home without professional assistance.

Additionally, feedback from the focus group (Section 2d) highlighted the desire patients have for an additional option to treat HS.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

In the BE HEARD trials, bimekizumab was associated with some side effects but, overall, the side effects observed were in line with what is already known about the safety of bimekizumab for the treatment of other diseases. The BE HEARD trials included patients who took placebo up to week 16, which provided a reference point for assessing the efficacy of bimekizumab. After week 16, patients switched from placebo to bimekizumab and so there are no placebo data after week 16. This means that, although the trial measured bimekizumab data up to week 48, it is challenging to compare bimekizumab to other treatments using these longer-term data.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects HS

The economic model was designed to capture the essential characteristics of HS and its treatment in UK clinical practice. Patients in the model are treated with three different options: bimekizumab, secukinumab, or best supportive care. The patient's condition is tracked over their lifetime based on their response to treatment. All symptoms related to the disease and any treatment events are recorded and captured in the model.

Modelling how bimekizumab improves HiSCR response
The model uses clinical trial data to generate response levels for patients receiving treatment with bimekizumab, secukinumab, or BSC. It calculates the proportion of patients who fall into each response category. When patients respond well to treatment, they continue to receive benefits and can improve their HiSCR level. The treatment that results in the highest number of patients achieving high response levels is considered to have the highest efficacy.

Modelling how bimekizumab improves quality of life
The model counts the time spent on each HiSCR level and rewards patients with a benefit for that duration, weighted by each HiSCR level.

Modelling how the costs of treatment differ with bimekizumab
The model counts the time patients receive treatment and adds all the costs (including background medication and administration). The model also adds costs for managing the disease and other routine care.

Cost-effectiveness results
Overall, the results of the analysis show that bimekizumab is a potential option for the NHS for the treatment of moderate to severe HS. NICE will evaluate the company's model findings to determine whether they believe the submitted information indicates potential cost savings compared to best supportive care.

Uncertainty
As clinical trials are typically conducted for a limited period, lifetime estimates for patients had to be generated by extrapolating the outcomes. However, such an analysis introduces a degree of uncertainty in the results. To ensure the accuracy of the model variables and assumptions, extensive testing was carried out, and the results were found to be robust.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a ‘step change’ in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Innovation in patient care
Current biological therapies for HS inhibit either IL-17A (but not IL-17F), or another protein called tumour necrosis factor. For a substantial proportion of

patients, these therapies are not effective or stop working. Bimekizumab is an innovative, alternative treatment option that inhibits IL-17F in addition to IL-17A. By reducing the activity of both of these key inflammatory proteins, bimekizumab can reduce inflammation and improve disease symptoms.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

The prevalence of HS is higher among women than men [1, 10, 11, 83], and among people with an African–Caribbean background compared with those with a European background [84]. It is not anticipated that this appraisal will exclude from consideration any people protected by the equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on health technology assessment (HTA) and the role of patient groups

- EUPATI guidance on patient involvement in HTA: https://www.eupati.eu/guidance-patient-involvement/
- International Network of Agencies for Health Technology Assessment: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence,

and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

Patient groups and charities

- British Skin Foundation: https://www.britishskinfoundation.org.uk/
- British Association of Dermatologists: https://www.bad.org.uk/pils/hidradenitis-suppurativa/
- HS Ireland: https://hsireland.ie/

Further information about HS

- NHS general information: https://www.nhs.uk/conditions/hidradenitis-suppurativa/
- Primary Care Dermatology Services general information: https://www.pcds.org.uk/clinical-guidance/hidradenitis-suppurativa
- Patient information: https://patient.info/skin-conditions/hidradenitis-suppurativa-leaflet

Further information about bimekizumab

- BE HEARD I trial information: https://clinicaltrials.gov/study/NCT04242446
- BE HEARD II trial information: https://www.clinicaltrials.gov/study/NCT04242498?term=be%20heard%20ii&rank=1

Further information on NICE and the role of patients**:**

- Public Involvement at NICE: https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement
- NICE's guides and templates for patient involvement in HTAs: https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement/support-for-vcs-organisations/help-us-develop-guidance/guides-to-developing-our-guidance
- EFPIA – Working together with patient groups (PDF): https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative: https://nationalhealthcouncil.org/issue/value/

4b) Glossary of terms

Abscesses. Red, tender, pus-containing cavities in the skin, typically accompanied by swelling and inflammation in the surrounding area.

Acne. A prevalent skin condition characterised by the presence of blackheads, whiteheads as well as pustules, which are filled with pus.

Biological therapy. A treatment that stimulates the body's immune system to fight disease.

Clinical effectiveness. The extent to which a healthcare intervention achieves the desired outcomes, such as improving health, relieving symptoms, or preventing disease, in a clinical setting.

Disease flares. A sudden and often temporary worsening of symptoms associated with a chronic illness or condition. It typically involves a rapid onset of symptoms that may include increased pain, inflammation, fatigue, or other manifestations of the underlying disease.

Draining tunnels. Also known as draining fistulae or sinus tracts. In patients with HS, tunnels can form under the skin due to chronic inflammation and can cause pain, discomfort, and increase the risk of complications. When these tunnels leak pus they are called draining tunnels.

Economic model. A way to predict the costs and effects of a treatment over time in a specific population of interest.

Efficacy. The effectiveness of a treatment observed in a clinical trial.

Hidradenitis Suppurativa Clinical Response (HiSCR). A standardised measure used in clinical trials and research to assess the effectiveness of treatments for hidradenitis suppurativa (HS).

Inflammation. A bodily response to injury or disease, which can lead to swelling and reddening of the skin.

Marketing authorisation. Approval by a regulatory body for a medicine or medical device to be used by patients in a specific place or country.

Monoclonal antibody. A type of protein produced in the laboratory that can target and bind to specific substances in the body, such as proteins or cells. These antibodies are designed to mimic the immune system's natural ability to fight off harmful invaders, and they are used in various medical treatments, including cancer therapy and autoimmune diseases.

Patient-reported outcomes (PROs). Structured patients' feedback which includes various dimensions of patients' experiences, including symptoms, treatment satisfaction, medication adherence, and overall quality of life. These outcomes are frequently assessed in clinical trials using validated tools to gauge the treatment's impact from the patient's perspective.

Protein. A large, complex molecule composed of one or more chains of amino acids. Proteins play essential roles in the structure, function, and regulation of cells and tissues in living organisms. They are involved in various biological processes, including enzymatic reactions, cell signalling, immune response, and structural support.

Pus. A dense, yellowish or greenish fluid that develops at the location of a confirmed infection.

Quality of life (QoL). The subjective assessment of an individual's overall well-being and satisfaction with various aspects of their life, particularly as it relates to their health status and healthcare interventions. It encompasses physical, mental, emotional, and social dimensions and is influenced by factors such as health status, functional ability, symptoms, psychological well-being, social relationships, and environmental factors.

Quality-adjusted life year (QALY). A comprehensive measure to assess the effectiveness of an intervention by quantifying both the improvements in quality of life and the extension of life expectancy associated with it. Incremental QALYs, compared with incremental costs, are utilised to determine the economic value of interventions. By encompassing various domains of quality of life, QALYs enable comparability across different disease areas, facilitating broad resource allocation decisions.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Bimekizumab for treating moderate to severe hidradenitis suppurativa [ID6134]

Clarification request

June 2024

File name	Version	Contains confidential information	Date
ID6134 Bimekizumab - EAG clarification request for company 18.06.24 [CON]	V1.0	Yes	24 June 2024

Results for analyses using the bio-naïve and bio-experienced models for questions B2, B7, and B17 in company response to clarification questions

Please find below results tables for the bio-experienced and bio-naïve subgroups. The models that generated these results have been supplied with this response. In the bio-experienced analyses (Table 1), bimekizumab (BKZ) showed improved cost-effectiveness versus secukinumab (SEC) and decreased cost-effectiveness vs. best supportive care (BSC) vs. the analyses presented in the company response to clarification (Table 3). Table 2 shows BKZ cost-effectiveness improving vs. BSC and decreasing vs. SEC in the treatment naïve population. In the majority of scenarios BKZ is cost-effective in pairwise comparisons to SEC and BSC.

Table 1 Results of scenario analyses using the bio-experienced subgroup transition probabilities

Scenario	Treatment	Total		Incremental		ICER (£/QALY) (BKZ vs comparator)
		Costs	QALYs	Costs	QALYs	
Base Case: overall population	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,531
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£2,319
	BKZ	[redacted]	[redacted]			
B2: SEC stopping rule in HiSCR<25 state = [redacted] to week 48	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,531
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£2,374
	BKZ	[redacted]	[redacted]			
B7: Use the same utility values for active treatment and BSC for HiSCR>75	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£13,839
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£2,205
	BKZ	[redacted]	[redacted]			
B17a: BSC slow long term loss of response	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£58,522
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£25,605
	BKZ	[redacted]	[redacted]			
B17b: BSC transition probabilities determined by NMA beyond week 16 (Company Submission scenario 7)	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£102,763
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£51,915
	BKZ	[redacted]	[redacted]			

Table 2 Results of scenario analyses using the bio-naïve subgroup transition probabilities

Scenario	Treatment	Total		Incremental		ICER (£/QALY) (BKZ vs comparator)
		Costs	QALYs	Costs	QALYs	
Base Case: overall population	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,061
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,939
	BKZ	[redacted]	[redacted]			
B2: SEC stopping rule in HiSCR<25 state = [redacted] to week 48	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,061
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£4,205
	BKZ	[redacted]	[redacted]			
B7: Use the same utility values for active treatment and BSC for HiSCR>75	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£11,370
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,713
	BKZ	[redacted]	[redacted]			
B17a: BSC slow long term loss of response	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£48,997
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£25,320
	BKZ	[redacted]	[redacted]			
B17b: BSC transition probabilities determined by NMA beyond week 16 (Company Submission scenario 7)	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£85,726
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£47,454
	BKZ	[redacted]	[redacted]			

Table 3 Results of scenario analyses using the overall transition probabilities

Scenario	Treatment	Total		Incremental		ICER (£/QALY) (BKZ vs comparator)
		Costs	QALYs	Costs	QALYs	
Base Case: overall population	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,444
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,605
	BKZ	[redacted]	[redacted]			
B2: SEC stopping rule in HiSCR<25 state = [redacted] to week 48	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,444
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,820
	BKZ	[redacted]	[redacted]			
B7: Use the same utility values for active treatment and BSC for HiSCR>75	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£11,754
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,404
	BKZ	[redacted]	[redacted]			
B17a: BSC slow long term loss of response	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£50,546
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£25,334
	BKZ	[redacted]	[redacted]			
B17b: BSC transition probabilities determined by NMA beyond week 16 (Company Submission scenario 7)	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£88,491
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£48,159
	BKZ	[redacted]	[redacted]			

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Single Technology Appraisal

Bimekizumab for treating moderate to severe hidradenitis suppurativa [ID6134]

Clarification questions – UCB responses

June 2024

File name	Version	Contains confidential information	Date
ID6134 Bimekizumab – UCB responses to clarificationv1.0 [REDACTED]	V1.0	No	03 June 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Systematic literature review

A1. Please justify the apparent inconsistency in the critical appraisal of studies included in the SLR (Table 115). The text above Table 115 states that SHARPS was assessed as "some concerns", attributable to bias in the selection of the reported result as authors performed unplanned *post hoc* analyses. However, data from BE HEARD I and II are from the *post hoc* HS-ABX analyses, rather than the prespecified analysis plan (All-ABX), therefore, should also be assessed as "some concerns".

In addition to the post hoc analyses for SHARPS, there were also some concerns about whether all conducted analyses had been reported. The statistical analysis plan reported that "*A Per-protocol Population (PP) … will be defined if deemed necessary … and the PP population, if defined, will be used for the efficacy analysis.*" However, it is unclear under what circumstances these analyses would be conducted, and whether these analyses were performed. Post hoc analyses were reported for a subgroup excluding patients who did not meet the key lesion entry criterion (abscess and inflammatory nodules [AN] count ≥3 within the HS nonsurgical sites at baseline), however this may not be identical to a PP analysis. In addition, the change in analyses for BE HEARD studies do not reflect any concerns with the trials

and do not alter the population, only the data handling methodologies to align closer with real world practice and to reduce heterogeneity in the network to allow for indirect comparison with secukinumab phase 3 evidence.

HS and the decision problem

A2. The company submission (CS) reports the prevalence of hidradenitis suppurativa (HS) as 0.8%, which appears to be based on sources using self-reported data. Please justify the use of self-reported data as the source of your prevalence figure of 0.8%. If possible, please also provide estimates of the proportion of the general population:

a) Who have moderate HS

b) Who have severe HS

c) Who will be eligible for bimekizumab.

The primary source of prevalence data that UCB uses is not a study which relies on self-reported data. The source cited for the prevalence of HS in the UK is a rigorous epidemiological study conducted by Ingram et al. [1]. This study used 4,364,308 records in the UK Clinical Practice Research Datalink (CPRD) Hospital Episode Statistics (HES) datalink (CPRD-HES) to identify 23,353 physician diagnosed HS cases, and then used clinical data to identify 10,146 additional patients who met strict HS diagnostic criteria, resulting in a prevalence of 0.77% [1]. Table 1 shows the criteria used to identify probably HS cases in the CPRD-HES data.

Table 1 Description of algorithms used to identify proxy hidradenitis suppurativa cases in the Clinical Practice Research Datalink (Ingram et al. 2018, Table 1) [1]

Subalgorithm	Description
1a	≥ 5 boils, furuncles, carbuncles or abscesses in flexural skin sites
1b	1–4 boils in flexural sites and ≥ 5 boils in total
1c	≥ 5 boils in unspecified skin sites
2a	'Multiple boils' and ≥ 1 flexural boil
2b	'Multiple boils' and no flexural lesion specified
3	'Drainage or incision of boil of skin' and ≥ 5 boils in total
4	Surgical excision/laser destruction of flexural skin
5a	≥5 short courses of oral flucloxacillin/ erythromycin/clarithromycin and ≥ 1 flexural boil, excluding eczema/skin ulcer/cellulitis

5b	≥ 5 short courses of oral flucloxacillin/ erythromycin/clarithromycin and ≥ 1 boil in unspecified skin site, excluding eczema/skin ulcer/cellulitis

The algorithms were used to identify 68,890 possible cases of HS in the CPRD. To validate the algorithm, a questionnaire was sent to primary care physicians. After validation, 10,146 patients met the stringent criteria established.

As described in the budget impact analysis submission, the bimekizumab target population is adults with moderate to severe HS who are contraindicated or inadequate responders to a prior biologic treatment (adalimumab). Adults (aged 18 and above) represent 79.25% of the overall England and Wales population [2, 3]. Real-world data suggest that 45.3% of people with HS have moderate to severe disease, defined as Hurley stage II or III [4]. This equates to a prevalence of adult HS patients who have moderate to severe disease of 0.28%. Among these patients it is estimated that only 2,456 would be considered for bimekizumab, resulting in an estimated eligible prevalence of 0.004%.

A3. The decision problem was restricted to patients who have failed to respond to adalimumab or who are otherwise unsuitable of adalimumab treatment. Please therefore present a justification for the presentation of data on biologic-naïve patients that predominates throughout the submission.

UCB have not presented any analyses of the biologic-naïve subgroup. All analyses presented, except for the biologic-experienced subgroup analyses, use data from all patients in the trials. The BE HEARD trials included 191/1014 (18.8%) biologic-experienced patients [5]. The SUNSHINE and SUNRISE trials included 255/1084 (23.5%) patients who were biologic experienced [6]. The clinical data presented are consistent with the network meta-analysis.

An analysis of the biologic-experienced subgroup in the BE HEARD trials found that bimekizumab demonstrated consistent efficacy in achieving and maintaining HiSCR response to week 48 irrespective of prior biologic use [5]. TA935 (secukinumab for the treatment of moderate to severe HS) reported broadly consistent results in patients with and without previous exposure to biologic treatment for HiSCR50 in the SUNRISE and SUNSHINE trials and the committee concluded that results of the full trial population were generalisable to the company's narrower (post-adalimumab)

target population [7]. In line with TA935, UCB have also conducted base case and scenario analyses based on the entire study population.

Using biologic-experienced data for the model was not feasible, as insufficient outcome data were reported from secukinumab trials to allow comparison based on HiSCR75 and HiSCR90 at the time the systematic review of efficacy was conducted. Secukinumab data in the biologic-experienced population was published for HiSCR75 after the completion of the systematic review, but it remains infeasible to inform the model health states using available data from the biologic-experienced NMA due to no HiSCR90 data for secukinumab being available. [6].

In question A21, we provide updated NMA results that include SUNSHINE and SUNRISE data for the biologic-experienced population for several outcomes, including HiSCR75. In question B16, UCB provide an economic model scenario that uses bimekizumab transition probabilities to week 48 derived from the biologic-experienced population in the BE HEARD studies.

A4. The company states that best supportive care may include “some adalimumab use due to limited treatment options” (CS Table 1). Given the decision problem population definition as those for whom adalimumab is inadequately effective or unsuitable, please clarify the circumstances in which adalimumab could be given to the decision problem population.

UCB conducted two advisory boards with 10 UK dermatologists participating and consulted a clinical advisor (not an advisory board participant) in the review of the company submission dossier. There was general agreement that a proportion of patients that do not initially achieve HiSCR25 response or who lose HiSCR25 response would continue to receive adalimumab. The clinical advisor consulted for the company submission review stated that the 20.8% figure from the Global VOICE study used for the proportion of patients who would receive adalimumab after failing all other treatments was appropriate [8].

Clinicians consulted in advisory boards supported that being on biological therapies was beneficial for patients even after losing HiSCR25 response. UCB have assumed that adalimumab would be the therapy used in this circumstance because assuming that a proportion of patients would receive secukinumab or bimekizumab would bias

the economic model. While patients may not regain response levels in the long-run after secondary non-response, it is likely that they would see some benefit from treatment. Table 2, below, shows that over time, patients have improvement in abscess and inflammatory nodule count when treated with bimekizumab even when they do not meet or no longer meet the HiSCR25 response criteria.

Table 2 Mean percentage reduction in abscess and inflammatory nodules (AN) by trial phase

	Weeks 2-16		Weeks 20-48	
	BKZ 320mg Q2W (SD)[number of observations]	BKZ 320mg Total (SD)[number of observations]	BKZ 320mg Q2W/Q4W (SD)[number of observations]	BKZ 320mg Total (SD)[number of observations]
<HiSCR25	[redacted]	[redacted]	[redacted]	[redacted]

A5. The NICE scope includes outcomes for inflammation/fibrosis and disease progression, but these have not been presented in the submission. Please justify the absence of these outcomes.

The outcomes for inflammation/fibrosis and disease progression have not been presented within the submission as these outcomes were not measured in the BE HEARD clinical trials and so no evidence is available.

Characteristics of the BE HEARD trials

A6. The EAG notes some concerns with possible imbalance in the BE HEARD trials between arms, particularly for disease duration, body weight, geographical region, AN count and DT count at baseline. Could the company please:

a) Provide a detailed description of the randomisation process in the BE HEARD trials.

Eligible study participants were randomised in a 2:2:2:1 ratio for treatment (bimekizumab 320mg Q2W/Q2W, bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, placebo/bimekizumab 320mg Q2W). Because of differences in the dosing schedules (Q2W and Q4W) and in order to maintain blinding, all study participants received 2 subcutaneous injections Q2W from Week 0 to Week 46.

An Interactive Response Technology (IRT) system was used for assigning eligible study participants to a treatment regimen at baseline based on a predetermined production randomisation and/or packaging schedule provided by UCB (or designee). The randomisation schedule was produced by the IRT vendor. The IRT generated individual assignments for kits of IMP, as appropriate, according to the visit schedule.

To enrol a study participant at Screening, the Investigator or designee contacted the IRT and provided brief details about the study participant to be enrolled. Each study participant received a unique number assigned at Screening that served as the study participant identifier throughout the study.

To randomise a study participant, the Investigator or designee contacted the IRT and provided brief details about the study participant to be randomised, including information regarding stratification factors (Hurley stage and baseline antibiotic use). The IRT automatically informed the Investigator or designee of the study participant's randomisation number. The IRT allocated kit numbers to the study participant based on the study participant number during the course of the study.

b) Comment on how imbalances in disease duration, body weight, geographical region, AN count and DT count might have occurred.

Randomisation in the studies was stratified by Hurley stage and baseline antibiotic use. This procedure ensured reasonable balance across treatment arms for those two variables. However, there were no such constraints for other baseline variables. Therefore, it is possible that some imbalances would be seen across two studies, four treatment arms, and a wide range of baseline variables. The imbalances for the variables noted are therefore attributed to chance.

c) Comment on the impact on interpretation of the trial results

Despite imbalances for the variables noted, clinically meaningful improvements in the primary endpoint were observed for both dose regimens compared with placebo across all subgroups, as shown in section B.2.7 and Appendix E of the company submission.

A7. Please provide further information about prior biologic use for HS in Table 11, i.e., the number of prior biologics received, and name of biologics received (rather than just 'Yes' or 'No' for 'Prior biologic use for HS').

a) If possible, please supply numbers of patients who were:

1. Contraindicated to adalimumab
2. Who had no response or inadequate response to adalimumab
3. Who developed secondary failure while taking adalimumab

Please find below a summary of prior biologic use within the BE HEARD I and II studies. Note that patients who have taken multiple prior biologics will contribute to the counts in more than one row.

Table 3 Prior biologic use in BE HEARD I (Safety Set)

Biologic	Placebo n=72 (%)	BKZ Q2W n=286 (%)	BKZ Q4W n=143 (%)	BKZ total n=429 (%)	All n=501 (%)
Adalimumab	17 (23.6)	65 (22.7)	30 (21.0)	95 (22.1)	112 (22.4)
Infliximab	5 (6.9)	13 (4.5)	8 (5.6)	21 (4.9)	26 (5.2)
Guselkumab	1 (1.4)	6 (2.1)	3 (2.1)	9 (2.1)	10 (2.0)
Ustekinumab	0	4 (1.4)	0	4 (0.9)	4 (0.8)
Iscalimab	0	2 (0.7)	0	2 (0.5)	2 (0.4)
Canakinumab	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Certolizumab	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Secukinumab	1 (1.4)	1 (0.3)	0	1 (0.2)	2 (0.4)
Etanercept	1 (1.4)	2 (0.7)	1 (0.7)	3 (0.7)	4 (0.8)

Table 4 Prior biologic use in BE HEARD II (Safety Set)

Biologic	Placebo n=74 (%)	BKZ Q2W n=290 (%)	BKZ Q4W n=142 (%)	BKZ total n=432 (%)	All n=506 (%)
Adalimumab	9 (12.2)	37 (12.8)	16 (11.3)	53 (12.3)	62 (12.3)
Infliximab	0	8 (2.8)	1 (0.7)	9 (2.1)	9 (1.8)
Guselkumab	0	3 (1.0)	0	3 (0.7)	3 (0.6)
Ustekinumab	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Secukinumab	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Risankizumab	1 (1.4)	0	0	0	1 (0.2)
Anakinra	0	1 (0.3)	0	1 (0.2)	1 (0.2)

No data were collected at baseline regarding participants who were contraindicated to adalimumab, had no response or inadequate response to adalimumab or who developed secondary failure while taking adalimumab.

A8. Please provide details on the reasons why patients discontinued from BE HEARD I and II owing to 'other' reasons (Figures 43 and 44 of the Appendices).

Discontinuation from BE HEARD I and II owing to 'other reasons' (n=20) were relocation away from clinic (n=12); schedule of study too demanding (n=2); principal investigator decision (n=1), sponsor decision (n=2); developed illness that would interfere with continued participation (n=1); AE with acne vulgaris and impetigo requiring systemic treatment not compatible with protocol (n=1); and withdrawn due to Ex#8 (n=1)

A9. (CS Section B.2.4.4) "With a 2-sided significance level of 0.025, for both trials the sample size provided 73% power for detecting at least a difference of 1.5 (bimekizumab Q4W vs placebo) for the worst skin pain change from baseline endpoint." This implies the trials were powered using pain rather than the HiSCR primary endpoint. Is this correct, and if so, why where the trials not powered for the primary endpoint?

a) Please supply a post-hoc power calculation to demonstrate the power of the BE HEARD trials to detect a suitable improvement in HiSCR50.

The BE HEARD trials were *a priori* powered for the primary endpoint of HiSCR50. The analysis of the primary efficacy endpoint and secondary efficacy endpoints (HiSCR75, Flare [BE HEARD II only], DLQI CFB, Worst Skin Pain CFB, Worst Skin Pain Response) were based on a comparison of bimekizumab versus placebo at Week 16, using an alpha adjustment strategy.

The power to detect a statistically significant difference for each of the primary and secondary endpoints is shown below:

Table 5 Power calculations for BE HEARD studies

	Power α = 0.025, 2-sided		Assumptions		
	Q2W	Q4W	Week 16 Bimekizumab Q2W N=280	Week 16 Bimekizumab Q4W N=140	Week 16 Placebo N=70
HiSCR50	0.99	0.90	Proportion Responders = 0.60	Proportion Responders = 0.50	Proportion Responders = 0.25
HiSCR75	0.99	0.98	Proportion Responders = 0.45	Proportion Responders = 0.35	Proportion Responders = 0.10
Flare [BE HEARD II Only]	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 CFB	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	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[a]	0.95	0.53	Proportion Responders = 0.53	Proportion Responders = 0.43	Proportion Responders = 0.23

[a] Assumes N=208, 104, 52 in Q2W, Q4W, and placebo, respectively, to account for Worst Skin Pain score at or above 3 (ie, the threshold for clinically meaningful change from Baseline).

A10. (CS Table 14) Can you please suggest why the use of antibiotic rescue was much higher for the BE HEARD I placebo arm than the BE HEARD II placebo arm.

Despite the higher intercurrent event rate for the receipt of systemic antibiotic rescue medication in the placebo group in BE HEARD I (20.8%) versus BE HEARD II (8.1%), there was no clinically meaningful impact on the primary endpoint analysis for HiSCR50 at week 16 (Table 6). While the bimekizumab responder rates accounting for intercurrent events are higher in BE HEARD II than BE HEARD I, the placebo rates are also higher in BE HEARD II, resulting in treatment differences across the studies that are generally similar. Furthermore, to avoid potential confounding due to different intercurrent event rates, assessing raw response rates (based on observed cases and not accounting for intercurrent events) between BE HEARD I and BE HEARD II shows that the response rates for a given treatment group were similar across studies; placebo 36.9% vs 34.3%, respectively;

Bimekizumab 320 mg Q4W, 58.1% vs 60.2%, respectively; Bimekizumab 320 mg Q2W, 58.8% vs 61.9%, respectively (Table 6).

Table 6 Intercurrent event rate versus HiSCR50 response rate at week 16 (RS)

	PBO n (%)		BKZ 320 mg Q4W n (%)		BKZ 320 mg Q2W n (%)	
	BE HEARD I N=72	BE HEARD II N=74	BE HEARD I N=144	BE HEARD II N=144	BE HEARD I N=289	BE HEARD II N=291
Any systemic rescue antibiotic	15 (20.8)	6 (8.1)	22 (15.3)	18 (12.5)	49 (17.0)	44 (15.1)
Responder rate – Incorporating intercurrent events[a]	28.7	32.2	45.3	53.8	47.8	52.0
Responder rate – Observed cases[b]	24/65 (36.9)	24/70 (34.3)	72/124 (58.1)	80/133 (60.2)	151/257 (58.8)	164/265 (61.9)

BKZ=Bimekizumab; CSR= clinical study report; HiSCR= Hidradenitis Supportive Clinical Response; MCMC = Markov Chain Monte Carlo; PBO=placebo; Q2W= every 2 weeks, Q4W= every 4 weeks; RS=randomised set
a Primary method for intercurrent event/missing data handling. Intermittent missing data are imputed using multiple imputation with MCMC method followed by monotone regression for monotone missing data. Lesion accounts are imputed then dichotomized to obtain the response status. Participants who experience an intercurrent event are treated as nonresponders following the intercurrent event.
b Data are summarised as observed, and intercurrent events are not factored into response rates.

We recognise there may be differences in clinical practice across regions that could have contributed to these differences in antibiotic use. However, no clinically meaningful impact on the study outcomes, especially the primary endpoint at week 16 in the placebo-controlled treatment period was observed.

A11. Please justify the trial exclusion criterion of “more than 20 draining tunnels at baseline”.

Consistent assessment of lesions by investigators, particularly in large, multicentre trials, is an important issue for trials in HS. The importance of standardising the collection and assessment of lesions is because clinical outcome measures used to assess efficacy (HISCR, PGA, IHS4) are all based on the abscess, nodule and fistula counts.

Excluding patients with a large number of draining tunnels is necessary to ensure accuracy when assessing HiSCR. HiSCR, the only validated measure in HS completely accepted by regulators, requires a patient to have no increase in draining

fistula count from baseline to be labelled as a responder. This criterion of the HiSCR definition causes an increase of one fistula from baseline to make a responder become a non-responder for the primary efficacy endpoint, regardless of the magnitude of decrease in AN count that may occur. Due to the complexity of assessing draining fistulas, especially when there are multiple fistulas in the same anatomical region, allowing an unlimited number of draining fistulas reduces the accuracy and assessment of the draining fistula count which may consequently impact HiSCR accuracy.

Finally, this criterion is consistent with criteria used to define disease burden in the PIONEER trials of adalimumab [9] and the SUNRISE/SUNSHINE trials of secukinumab [10]. For these reasons, an upper limit of draining fistulas as specified in the exclusion criterion is commonly used in clinical trials.

A12. Patients and study investigators were blinded, but injections were administered unblinded as the bimekizumab and placebo agents looked different. This may have increased the risk of performance bias, directly or via contamination of patient blinding. Why was the placebo not made to look like bimekizumab?

Development of a placebo that would match the bimekizumab solution colour without using non-inert components and viscosity was not possible. Given that the HiSCR, IHS4 and flare outcomes are based on objective lesion measurements assessed by the study investigators (blinded), it is not expected that any performance bias would be introduced by injections being administered by unblinded personnel. Only unblinded personnel were able to record the visits, prepare the necessary material, report information related to the treatment and perform the administration as well as treatment follow-up. In addition, only blinded personnel ensured that the correct kit had been administered to the patient without access to the IMPs or documents that may contain unblinded information. The unblinded study site personnel were not involved in the study in any way other than assuring the agents were taken from the correct kit, prepared according to the handling manual and administered to the study participants. Inadvertent unblinding was listed as a major protocol deviation.

Clinical Effectiveness Results from BE HEARD I and II

A13. Please present separate demographics and baseline characteristics for patients who received BKZ 320 mg Q2W/Q2W and BKZ 320 mg Q2W/Q4W in Table 11 (i.e., columns 4 and 8).

Table 7 Demographics and baseline characteristics in BE HEARD I and II (RS)

Category	BE HEARD I		BE HEARD II	
	BKZ 320 mg Q2W/Q4W n = 146	BKZ 320 mg Q2W/Q2W n = 143	BKZ 320 mg Q2W/Q4W n = 146	BKZ 320 mg Q2W/Q2W n = 145
Study participant characteristics				
Age, years, mean ± SD	36.9 ± 12.5	36.9 ± 12.3	37.1 ± 12.3	36.8 ± 12.4
Gender, n (%)				
Male	55 (37.7)	58 (40.6)	63 (43.2)	78 (53.8)
Female	91 (62.3)	85 (59.4)	83 (56.8)	67 (46.2)
Body weight, kg, mean ± SD	96.6 ± 25.4	97.9 ± 25.3	95.3 ± 22.5	95.6 ± 25.9
≤ 100 kg, n (%)	83 (56.8)	85 (59.4)	99 (67.8)	93 (64.1)
> 100 kg, n (%)	62 (42.5)	56 (39.2)	47 (32.2)	52 (35.9)
BMI, kg/m^2, mean ± SD	33.23 ± 8.11	33.49 ± 8.54	32.12 ± 7.57	31.90 ± 8.51
Smoking status, n (%)				
Never	55 (37.7)	56 (39.2)	49 (33.6)	57 (39.3)
Current	61 (41.8)	66 (46.2)	73 (50.0)	61 (42.1)
Former	24 (16.4)	19 (13.3)	23 (15.8)	26 (17.9)
Racial group, n (%)				
White	119 (81.5)	114 (79.7)	114 (78.1)	118 (81.4)
Black	19 (13.0)	22 (15.4)	12 (8.2)	10 (6.9)
Asian [a]	2 (1.4)	0	11 (7.5)	11 (7.6)
Geographical region, n (%)				
North America	66 (45.2)	66 (46.2)	42 (28.8)	36 (24.8)
Central/Eastern Europe	13 (8.9)	17 (11.9)	56 (38.4)	67 (46.2)
Western Europe	50 (34.2)	50 (35.0)	39 (26.7)	29 (20.0)
Asia/Australia	17 (11.6)	10 (7.0)	9 (6.2)	13 (9.0)
Duration of disease, years, Mean ± SD	8.68 ± 7.76	8.35 ± 7.51	7.89 ± 7.57	6.80 ± 7.16
Hurley stage (derived), n (%) [b]				
II	73 (50.0)	76 (53.1)	87 (59.6)	90 (62.1)
III	73 (50.0)	67 (46.9)	59 (40.4)	55 (37.9)
AN count, mean ± SD	16.94 ± 16.25	13.65 ± 9.66	17.54 ± 17.40	15.78 ± 13.24
Hurley stage II [c]	12.38 ± 13.18	11.78 ± 8.19	12.78 ± 7.64	13.26 ± 10.63
Hurley stage III [c]	21.49 ± 17.77	15.78 ± 10.76	24.56 ± 24.20	19.91 ± 15.92
DT count, mean ± SD	3.99 ± 4.78	4.03 ± 4.95	3.60 ± 4.06	3.61 ± 3.89
Hurley stage II [c]	1.62 ± 2.14	1.59 ± 2.32	1.89 ± 1.77	2.34 ± 2.62

Category	BE HEARD I		BE HEARD II	
	BKZ 320 mg Q2W/Q4W n = 146	BKZ 320 mg Q2W/Q2W n = 143	BKZ 320 mg Q2W/Q4W n = 146	BKZ 320 mg Q2W/Q2W n = 145
Hurley stage III [c]	6.36 ± 5.47	6.81 ± 5.65	6.14 ± 5.05	5.67 ± 4.69
IHS4 score, mean ± SD	36.6 ± 33.0	33.5 ± 27.5	35.5 ± 35.0	33.2 ± 23.3
HiSQOL total score, mean ± SD	24.48 ± 12.78	25.64 ± 13.15	24.48 ± 13.50	23.97 ± 12.22
Symptom score	8.09 ± 3.19	7.96 ± 3.58	7.84 ± 3.56	7.54 ± 3.15
Psychosocial score	5.01 ± 4.09	5.52 ± 4.42	4.98 ± 4.36	4.74 ± 3.94
Activities and adaptations score	11.38 ± 7.16	12.16 ± 6.84	11.66 ± 7.31	11.69 ± 6.69
DLQI total score, mean ± SD	11.1 ± 6.7	11.8 ± 6.5	10.5 ± 6.7	10.6 ± 6.4
HSSDD worst pain score, mean ± SD	5.40 ± 2.56	5.58 ± 2.54	5.33 ± 2.40	5.32 ± 2.43
Antibiotic use (derived), n (%) [d]				
Yes	14 (9.6)	13 (9.1)	14 (9.6)	16 (11.0)
No	132 (90.4)	130 (90.9)	132 (90.4)	129 (89.0)
Prior biologic use for HS, n (%) [e]				
Yes	37 (25.3)	38 (26.6)	19 (13.0)	21 (14.5)
No	109 (74.7)	105 (73.4)	127 (87.0)	124 (85.5)

[a] BE HEARD II included 28 Japanese participants. [b] Derived Hurley stage for each participant was the worst overall Hurley stage derived from the Hurley Stages recorded across all anatomical regions. [c] Derived Hurley stage. [d] Derived antibiotic use at baseline was defined as eCRF record of a stable dose and regimen of systemic antibiotic use for at least 28 days prior to baseline; otherwise, derived antibiotic use at baseline was defined as "No". [e] All prior biologic treatments received by patients were for HS;
AN, abscess and inflammatory nodule; BKZ, bimekizumab; BMI, body mass index; DLQI: Dermatology Life Quality Index; HiSQOL: Hidradenitis Suppurativa Quality of Life; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary; IHS4, International Hidradenitis Suppurativa Severity Score System; Q2W, every 2 weeks; Q4W, every 4 weeks; SD; standard deviation

A14. Table 12 in document B provides useful information on management of dropouts, but further clarification would be useful. Please:

a) explain the details of multiple imputation for continuous endpoints

b) explain the details of modified non-responder imputation for binary endpoints

The analyses for the primary and secondary efficacy variables (both continuous and binary) included the use of multiple imputation. If study participants had an intercurrent event as defined in CS Table 13, then the primary efficacy variable at that timepoint and all subsequent timepoints (whether the data were observed or not) was set to "nonresponse".

All remaining missing data for the endpoint were imputed using multiple imputation Markov-Chain Monte Carlo method (MI-MCMC)/monotone regression. In multiple imputation, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data were imputed using the Markov-Chain Monte Carlo method, followed by regression for monotone missing data. The multiple imputation procedures for the primary and secondary efficacy analyses are based on an assumption of data missing at random and were pre-specified in the statistical analysis plan.

For binary endpoints:

1. A dataset was created for each treatment group, with observed values and those needing estimation by multiple imputation. For the imputation step, a distinction was made between monotone and non-monotone missing values.

    a. Intermittent missing values in each data set were filled using the MCMC method with multiple chain, monotone missing data imputing pattern, and non-informative priors for all parameters. The first 200 iterations were discarded as burn-in. A total of 100 sets of imputations were performed. The resulting 100 imputed data sets had a monotone missing pattern and were imputed using the method for monotone missingness.

    b. Monotone missing data were imputed using monotone regression. A separate regression model was estimated for each variable with missing values (i.e., measurement at each timepoint). Based on the resulting model, a new regression model was then drawn and used to impute the missing values for the variable. As the dataset had a monotone missing pattern, the process was repeated sequentially for variables with missing values. The procedure was based on the 100 imputed datasets generated from the MCMC procedure and was performed by imputation.

    c. In each case, Hurley Stage at Baseline, Baseline antibiotic use, and the value of the variable of interest at Baseline and each post-baseline

visit (prior to the time point of interest) were included in the imputation model (in cases of non-convergence, baseline antibiotic use [and subsequently baseline Hurley stage] was dropped from the model on a case-by-case basis to achieve convergence). If the imputation model did not converge, last observation carried forward (LOCF) wasbe used. The resulting datasets for each treatment arm were combined into a complete dataset based on each of the 100 imputations.

d. For each complete imputed dataset, the dichotomous responder variable was computed. For e.g. HiSCR response, the imputation of each lesion type was performed separately. For HiSCR response, the AN, inflammatory nodule, abscess and draining tunnel counts in the imputed datasets were compared directly to the observed baseline counts to determine response status. If values outside of pre-defined ranges (e.g., <0 for lesion counts) were imputed, they were cut off as appropriate after the multiple imputation procedure but prior to deriving the response. Standard rounding rules were also applied to the imputed values of endpoint that can only take integer values (e.g., abscess count).

e. Estimated response rates and associated standard errors were obtained for each of the 100 imputed datasets (for instance, for logistic regression analyses, adjusted responder rates and associated standard errors were obtained from the logistic regression of each of the 100 imputed datasets; for unadjusted proportions of responders, these were calculated at each time point from the imputed datasets using PROC FREQ). These estimates were combined for overall inference using Rubin's rules in PROC MIANALYZE. Analysis was performed using SAS statistical software.

For continuous endpoints:

1. The MCMC/monotone regression method described above in Step 1 for binary endpoints was performed.

2. (For change from baseline summaries; if the value itself was being summarised, no additional derivation was needed): Based on the multiply imputed datasets obtained the for the given variable, the change from baseline was derived for each of the 100 complete imputed datasets based on the observed baseline value and the observed/imputed post-baseline values.

3. If a statistical model was being used for the analysis of the variable, then that was performed for each imputation. If no statistical model was being used, then simple descriptive statistics were calculated.

4. In general (hs-CRP was an exception), the following rules were applied: the results of the 100 imputed datasets (based on the statistical model or descriptive statistics) were combined with means and standard errors calculated using Rubin's rules (via PROC MIANALYZE). For the calculation of other descriptive statistics (e.g., median, minimum, maximum), Rubin's rules do not apply. For those, multiple imputation estimates were computed by simply averaging the estimates from the multiple repetitions of the imputation algorithm.

A15. Please clarify antibiotic use in the trial that was not counted as 'rescue'. For example, how many patients were taking long term stable doses to treat HS, and how many for non-HS infections?

Antibiotic use was allowed at baseline for study participants entering the studies in the antibiotic strata. Antibiotics were allowed if the patient's dose was a stable regimen of doxycycline, minocycline, or an equivalent systemic tetracycline for 28 days prior to Baseline and the dose and regimen was expected to remain stable throughout study participation, but at least through Week 16. Therefore, all antibiotic use at baseline would be considered a long-term stable dose of antibiotics to treat HS. The number of patients starting antibiotics for non-HS infections can be inferred from the antibiotic intercurrent event data shown in the response to A17b. The differential between the number of subjects who experienced an intercurrent event of any systemic antibiotic less those who experienced an intercurrent event of an HS specific rescue antibiotic is the number starting antibiotics for non-HS infections.

Table 8 Antibiotic use at baseline in BE HEARD I and II (RS)

	BE HEARD I			BE HEARD II		
	PBO N=72	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=289	PBO N=74	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=291
Antibiotic use at baseline	5 (6.9%)	8 (5.6%)	27 (9.3%)	6 (8.1%)	10 (6.9%)	30 (10.3%)

RS, randomised set.

A16. PRIORITY: Please provide the following results for the subgroup of biologic-experienced patients in each treatment group (including placebo) for the pooled BE HEARD population:

1. **A summary of baseline characteristics for this group (reporting the same characteristics as CS Table 11).**
2. **HiSCR50, 75, 90 and 100 responses, at 4-week intervals (as per Figures 7 and 8), with tabulated results at 16 weeks and 48 weeks.**
3. **Mean percentage change from baseline in AN lesion count, at 16 weeks and 48 weeks.**
4. **Mean absolute change in DT count and DT reduction ≥3 among patients with DT count ≥5 at baseline, at 16 weeks and 48 weeks.**
5. **IHS4 severity to week 48 (as presented in Figure 12) and IHS4-55 at 16 weeks and 48 weeks.**
6. **Proportion of patients with flare, at 16 weeks and 48 weeks.**
7. **Patient-reported outcomes (similar to Tables 25 to 32 but using the pooled BE HEARD I and BE HEARD II population and presenting each of the four treatment groups (Q2W/Q2W, Q2W/Q4W, Q4W/Q4W, placebo/BKZ Q2W).**
8. **Patient disposition (numbers dropping out and why)**

1. Patient baseline characteristics for the biologic-experienced subgroup are presented in Table 9.

Table 9 Patient baseline characteristics for the biologic-experienced subgroup (pooled BE HEARD population)

Category	Pooled BE HEARD population			
	Placebo n = 29	BKZ 320 mg Q4W n = 47	BKZ 320 mg Q2W n = 115	All Participants N = 191
Study participant characteristics				
Age, years, mean ± SD	39.5 ± 12.1	36.6 ± 10.3	38.6 ± 13.3	38.2 ± 12.4
Gender, n(%)				
Male	8 (27.6)	19 (40.4)	58 (50.4)	85 (44.5)
Female	21 (72.4)	28 (59.6)	57 (49.6)	106 (55.5)
Body weight, kg, mean ± SD	94.0 ± 27.0	103.2 ± 23.8	96.7 ± 26.5	97.9 ± 26.0
≤ 100 kg, n (%)	19 (65.5)	23 (48.9)	69 (60.0)	111 (58.1)
> 100 kg, n (%)	10 (34.5)	24 (51.1)	46 (40.0)	80 (41.9)
BMI, kg/m^2, mean ± SD	32.69 ± 8.67	35.38 ± 7.73	32.11 ± 7.95	33.00 ± 8.09
Smoking status, n (%)				
Never	11 (37.9)	16 (34.0)	32 (27.8)	59 (30.9)
Current	18 (62.1)	16 (34.0)	57 (49.6)	91 (47.6)
Former	0	15 (31.9)	26 (22.6)	41 (21.5)
Racial group, n (%)				
White	23 (79.3)	36 (76.6)	99 (86.1)	158 (82.7)
Black	4 (13.8)	3 (6.4)	6 (5.2)	13 (6.8)
Asian	1 (3.4)	2 (4.3)	2 (1.7)	5 (2.6)
Geographical region, n (%)				
North America	11 (37.9)	17 (36.2)	31 (27.0)	59 (30.9)
Central/Eastern Europe	6 (20.7)	8 (17.0)	27 (23.5)	41 (21.5)
Western Europe	11 (37.9)	20 (42.6)	50 (43.5)	81 (42.4)
Asia/Australia	1 (3.4)	2 (4.3)	7 (6.1)	10 (5.2)
Baseline disease characteristics				
Duration of disease, years, Mean ± SD	10.96 ± 8.58	9.57 ± 7.99	8.79 ± 7.79	9.31 ± 7.95
Hurley stage (derived), n (%) [b]				
II	11 (37.9)	18 (38.3)	42 (36.5)	71 (37.2)
III	18 (62.1)	29 (61.7)	73 (63.5)	120 (62.8)
AN count, mean ± SD	15.66 ± 8.71	20.47 ± 38.97	16.62 ± 13.51	17.42 ± 22.17
Hurley stage II [c]	16.45 ± 10.91	25.22 ± 62.09	12.36 ± 6.99	16.25 ± 31.81
Hurley stage III [c]	15.17 ± 7.37	17.52 ± 11.43	19.07 ± 15.64	18.11 ± 13.73
DT count, mean ± SD	5.21 ± 5.62	4.79 ± 5.31	5.84 ± 5.64	5.49 ± 5.55
Hurley stage II [c]	1.45 ± 2.11	1.50 ± 2.07	2.19 ± 2.81	1.90 ± 2.54
Hurley stage III [c]	7.50 ± 5.89	6.83 ± 5.70	7.95 ± 5.80	7.61 ± 5.76
IHS4 score, mean ± SD	39.9 ± 25.6	44.6 ± 48.0	44.6 ± 34.7	43.9 ± 37.1
HiSQOL total score, mean ± SD	28.46 ± 15.17	30.06 ± 13.54	27.83 ± 12.56	28.48 ± 13.18
Symptom score	8.86 ± 3.62	8.91 ± 3.20	8.58 ± 3.43	8.71 ± 3.39
Psychosocial	6.21 ± 4.54	6.43 ±	5.63 ± 4.01	5.91 ± 4.24

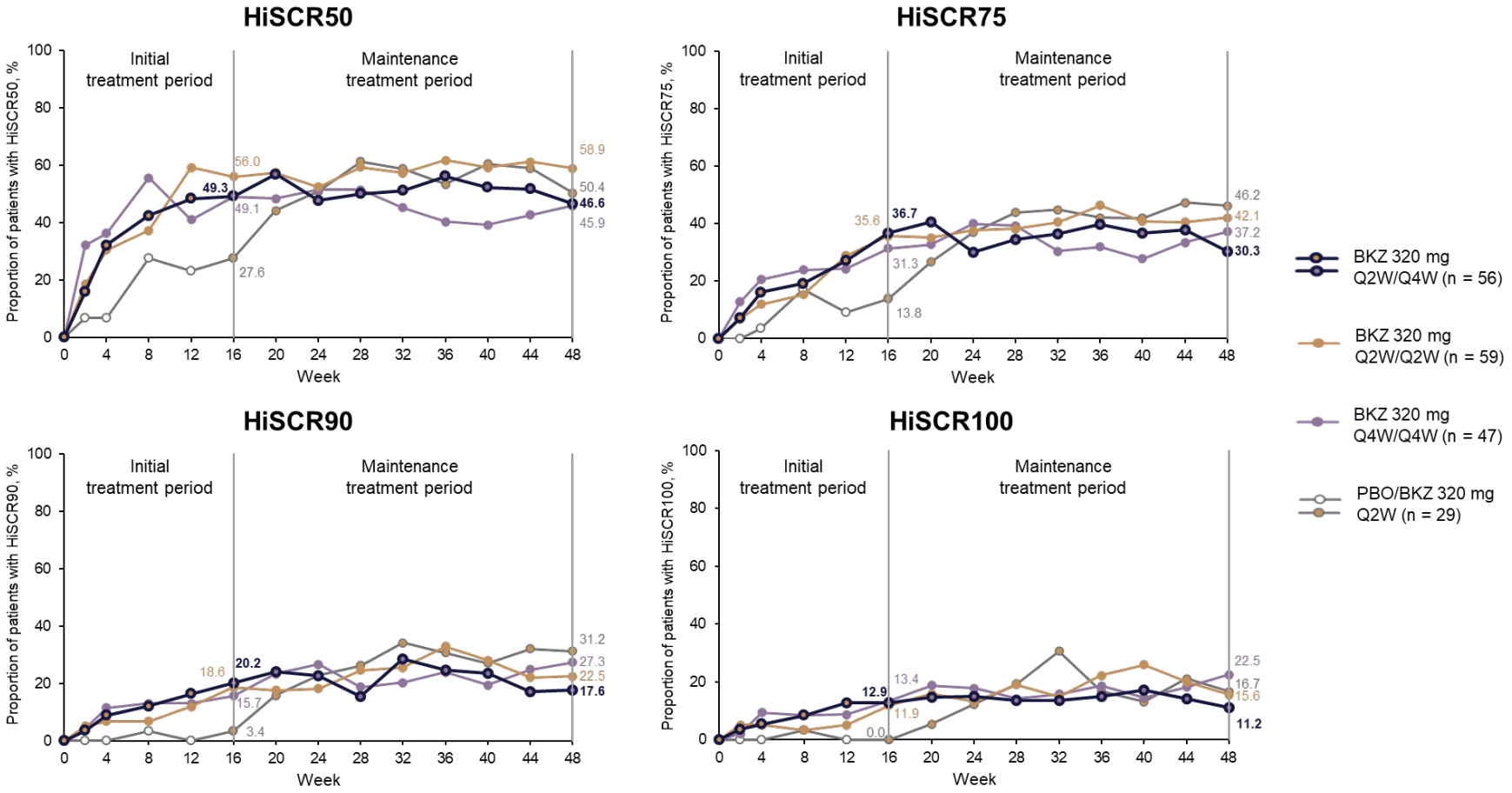
Category	Pooled BE HEARD population			
	Placebo n = 29	BKZ 320 mg Q4W n = 47	BKZ 320 mg Q2W n = 115	All Participants N = 191
score		4.61		
Activities and adaptations score	13.39 ± 8.55	14.72 ± 7.66	13.62 ± 6.76	13.86 ± 7.25
DLQI total score, mean ± SD	13.6 ± 8.1	13.6 ± 7.6	13.0 ± 6.8	13.2 ± 7.2
HSSDD worst pain score, mean ± SD	5.82 ± 2.59	5.88 ± 2.44	6.15 ± 2.32	6.04 ± 2.38
Antibiotic use (derived), n (%) [d]				
Yes	3 (10.3)	3 (6.4)	8 (7.0)	14 (7.3)
No	26 (89.7)	44 (93.6)	107 (93.0)	177 (92.7)
Prior biologic use for HS, n (%) [e]				
Yes	29 (100)	47 (100)	115 (100)	191 (100)
No	0	0	0	0

a BE HEARD II (overall population) included 28 Japanese participants. b Derived Hurley stage for each participant was the worst overall Hurley stage derived from the Hurley Stages recorded across all anatomical regions. c Derived Hurley stage. d Derived antibiotic use at baseline was defined as eCRF record of a stable dose and regimen of systemic antibiotic use for at least 28 days prior to baseline; otherwise, derived antibiotic use at baseline was defined as “No”. e All prior biologic treatments received by patients were for HS; two patients initially included in the ‘prior biologic use’ subgroup were switched to the ‘biologic-naive’ subgroup, as they had not received true biologic therapy.

AN, abscess and inflammatory nodule; BKZ, bimekizumab; BMI, body mass index; DLQI: Dermatology Life Quality Index; HiSQOL: Hidradenitis Suppurativa Quality of Life; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary; IHS4, International Hidradenitis Suppurativa Severity Score System; Q2W, every 2 weeks; Q4W, every 4 weeks; SD; standard deviation; TNFi, tumour necrosis factor inhibitor.

2. The following HiSCR data are presented for the biologic-experienced subgroup (pooled BE HEARD trial population):
    a. HiSCR50, 75, 90 and 100 responses, at 4-week intervals up to week 48 for mNRI for HS-ABX (as per Figures 7 in CS): Figure 1
    b. HiSCR50, 75, 90 and 100 responses, at 4-week intervals up to week 48 for OC (as per Figures 8 in CS): Figure 2
    c. Tabulated results at 16 weeks and 48 weeks for HiSCR50, HiSCR75, HiSCR90 and HiSCR100: Table 10

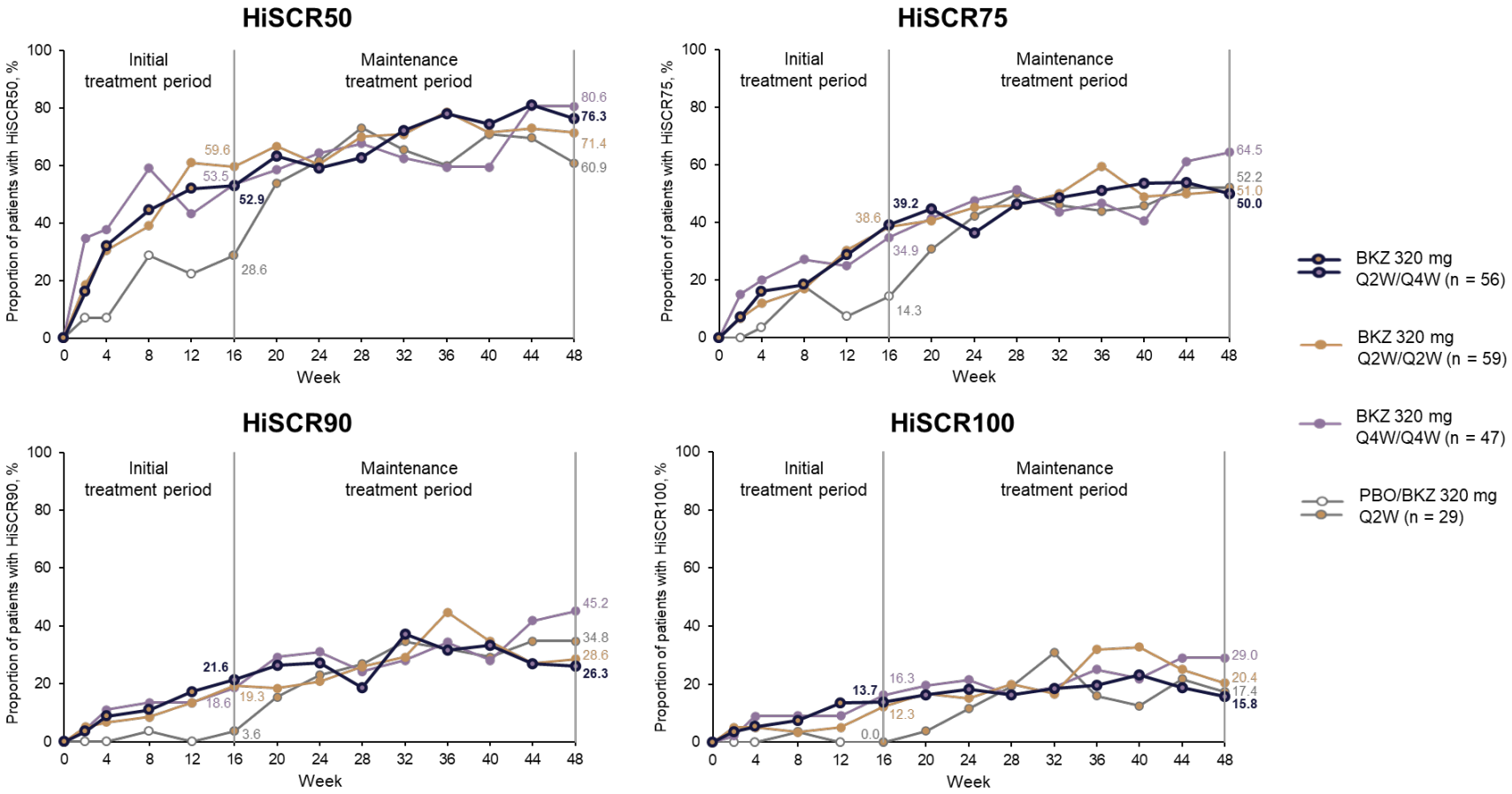
Figure 1. HiSCR50, HiSCR75, HiSCR90 and HiSCR100 responses up to week 48 in pooled BE HEARD population for the biologic-experienced subgroup (mNRI for HS-ABX)



mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.

ABX, antibiotics; HiSCR, hidradenitis suppurativa clinical response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; Q2W, every 2 weeks; Q4W, every 4 weeks.

Figure 2. HiSCR50, HiSCR75, HiSCR90 and HiSCR100 responses up to week 48 in pooled BE HEARD population for the biologic-experienced subgroup (OC)



OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.

HiSCR, hidradenitis suppurativa clinical response; HS, hidradenitis suppurativa; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 10 HiSCR50, HiSCR75, HiSCR90 and HiSCR100 responses for week 16 and week 48 in the biologic-experienced subgroup (pooled BE HEARD population)

HiSCR50 responder rates	PBO/BKZ 320 mg Q2W (n = 29)	BKZ 320 mg Q4W/Q4W (n = 47)	BKZ 320 mg Q2W/Q4W (n = 56)	BKZ 320 mg Q2W/Q2W (n = 59)
HiSCR50: Week 16				
mNRI for HS-ABX, % (95% CI)	27.6 (NC, NC)	49.1 (34.5, 63.8)	49.3 (36.0, 62.7)	56.0 (43.3, 68.6)
OC, n/N (%)	8/28 (28.6)	23/43 (53.5)	27/51 (52.9)	34/57 (59.6)
HiSCR50: Week 48				
mNRI for HS-ABX, % (95% CI)	50.4 (31.6, 69.2)	45.9 (30.3, 61.6)	46.6 (32.8, 60.5)	58.9 (45.9, 72.0)
OC, n/N (%)	14/23 (60.9)	25/31 (80.6)	29/38 (76.3)	35/49 (71.4)
HiSCR75: Week 16				
mNRI for HS-ABX, % (95% CI)	13.8 (NC, NC)	31.3 (17.8, 44.8)	36.7 (23.8, 49.5)	35.6 (NC, NC)
OC, n/N (%)	4/28 (14.3)	15/43 (34.9)	20/51 (39.2)	22/57 (38.6)
HiSCR75: Week 48				
mNRI for HS-ABX, % (95% CI)	46.2 (27.2, 65.1)	37.2 (22.5, 51.8)	30.3 (17.4, 43.2)	42.1 (29.0, 55.2)
OC, n/N (%)	12/23 (52.2)	20/31 (64.5)	19/38 (50.0)	25/49 (51.0)
HiSCR90: Week 16				
mNRI for HS-ABX, % (95% CI)	3.4 (NC, NC)	15.7 (5.0, 26.3)	20.2 (9.5, 30.8)	18.6 (NC, NC)
OC, n/N (%)	1/28 (3.6)	8/43 (18.6)	11/51 (21.6)	11/57 (19.3)
HiSCR90: Week 48				
mNRI for HS-ABX, % (95% CI)	31.2 (13.4, 49.0)	27.3 (13.6, 40.9)	17.6 (6.8, 28.5)	22.5 (11.4, 33.6)
OC, n/N (%)	8/23 (34.8)	14/31 (45.2)	10/38 (26.3)	14/49 (28.6)
HiSCR100: Week 16				
mNRI for HS-ABX, % (95% CI)	0 (NC, NC)	13.4 (3.4. 23.3)	12.9 (4.0, 21.8)	11.9 (NC, NC)
OC, n/N (%)	0/28	7/43 (16.3)	7/51 (13.7)	7/57 (12.3)
HiSCR100: Week 48				
mNRI for HS-ABX, % (95% CI)	16.7 (1.9, 31.4)	22.5 (9.7, 35.4)	11.2 (2.2, 20.1)	15.6 (5.9, 25.4)
OC, n/N (%)	4/23 (17.4)	9/31 (29.0)	6/38 (15.8)	10/49 (20.4)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.
BKZ, bimekizumab; CI, confidence interval; HiSCR, hidradenitis suppurativa clinical response; mNRI, modified non-responder imputation; NC, not calculable; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks.

3. Mean percentage change from baseline in AN lesion count, at 16 weeks and 48 weeks for the biologic-experienced subgroup (pooled BE HEARD population) is presented in Table 11.

Table 11 Percentage change from baseline in AN lesion count from baseline at week 16 and at week 48 in the pooled BE HEARD population for the biologic-experienced subgroup (MI for HS-ABX)

Visit	Placebo/BKZ 320 mg Q2W (n=29)	BKZ 320 mg Q4W/Q4W (n = 47)	BKZ 320 mg Q2W/Q4W (n = 56)	BKZ 320 mg Q2W/Q2W (n = 59)
Week 16, mean (SE)	−11.7 (11.5)	−48.4 (8.5)	−51.4 (6.5)	−53.6 (6.2)
Week 48, mean (SE)	−69.7 (6.7)	−61.2 (9.6)	−63.9 (6.3)	−70.6 (5.5)

MI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as having experienced an intercurrent event. Intermittent 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 multiple imputation method for missing data.
ABX, antibiotics; AN, abscess and inflammatory nodule; HS, hidradenitis suppurativa; MI, multiple imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.

4. Mean absolute change in DT count from baseline and DT reduction ≥3 among patients with DT count ≥5 at baseline, at 16 weeks and 48 weeks for the biologic-experienced subgroup (pooled BE HEARD population) are shown in Table 12.

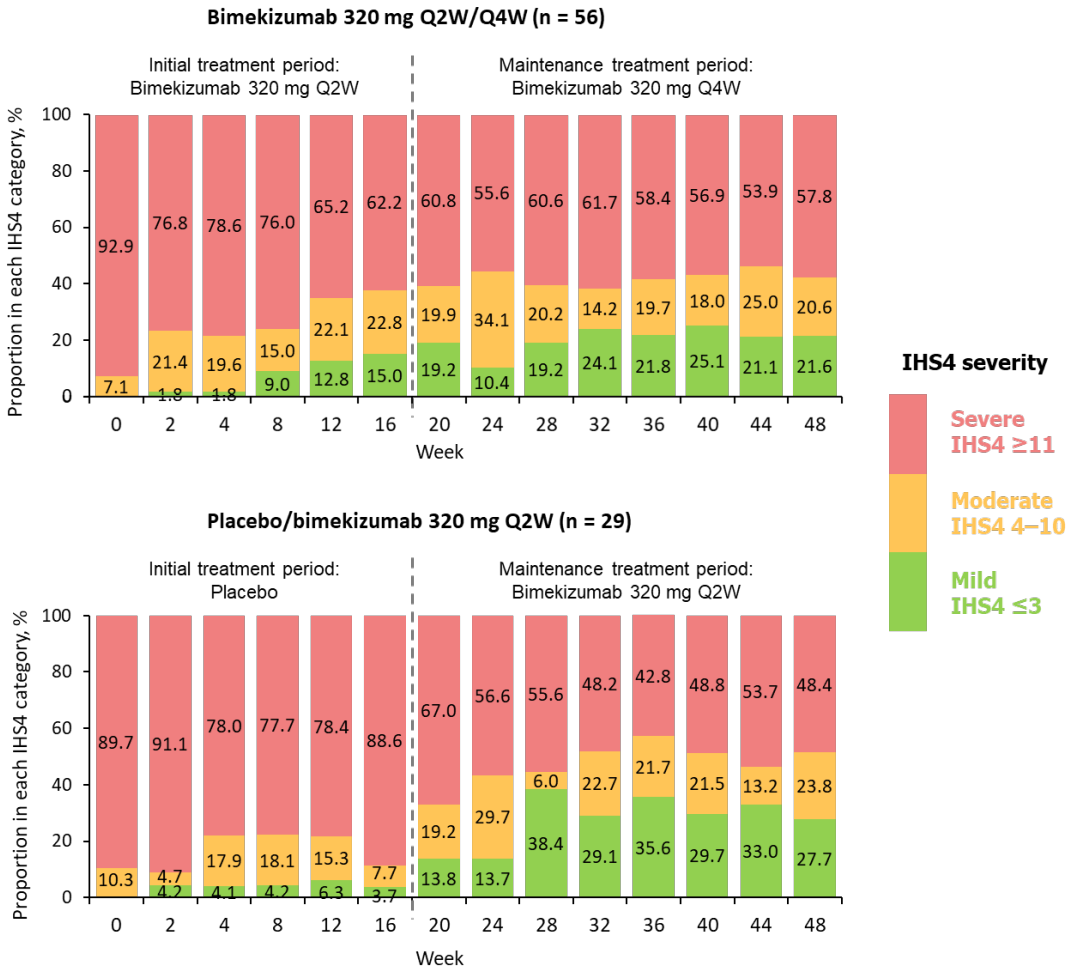
Table 12 Absolute change from baseline in DT count (MI for HS-ABX) and DT reduction ≥3 among patients with DT count ≥5 at baseline (mNRI for HS-ABX), at week 16 and at week 48 in the pooled BE HEARD population for the biologic-experienced subgroup

Visit	Placebo/BKZ 320 mg Q2W	BKZ 320 mg Q4W/Q4W	BKZ 320 mg Q2W/Q4W	BKZ 320 mg Q2W/Q2W
Absolute change from baseline in DT count (MI for HS-ABX), mean (SE)				
Baseline N	29	47	56	59
Week 16	0.0 (0.7)	−1.5 (0.5)	−2.0 (0.5)	−2.6 (0.5)
Week 48	−3.1 (0.9)	−2.6 (0.5)	−2.5 (0.6)	−3.7 (0.6)
Proportion of patients with a DT reduction ≥3 among patients with DT count ≥5 at baseline (mNRI for HS-ABX), % (95% CI)				
Baseline N	14	19	22	32
Week 16	14.3 (NC, NC)	45.8 (22.9, 68.7)	45.5 (NC, NC)	65.5 (49.0, 82.0)
Week 48	49.9 (23.7, 76.2)	47.3 (24.8, 69.8)	45.7 (24.7, 66.8)	70.8 (54.8, 86.8)

MI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as missing at all subsequent visits and imputed using the multiple imputation method for missing data.
mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
ABX, antibiotics; CI, confidence interval; DT, draining tunnel; HS, hidradenitis suppurativa; MI, multiple imputation; mNRI, modified non-responder imputation; NC, not calculable; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks.

5. The following IHS4 data are presented for the biologic-experienced subgroup (pooled BE HEARD trial population):
    a. IHS4 severity to week 48 (as presented in Figure 12 of the CS): Figure 3
    b. IHS4-55 responder rates at 16 weeks and 48 weeks: Table 13

Figure 3. IHS4 severity to week 48 in pooled BE HEARD population biologic-experienced subgroup (MI for HS-ABX)



MI for HS-ABX: Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as missing at all subsequent visits and imputed using the multiple imputation method for missing data. BKZ, bimekizumab; HS, hidradenitis suppurativa; IHS4, International HS Severity Scoring System; MI, multiple imputation; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 13 IHS4-55 responses at week 16 and week 48 in pooled BE HEARD population biologic-experienced subgroup (mNRI for HS-ABX; OC)

IHS4-55 responder rates	PBO/BKZ 320 mg Q2W (n = 29)	BKZ 320 mg Q4W/Q4W (n = 47)	BKZ 320 mg Q2W/Q4W (n = 56)	BKZ 320 mg Q2W/Q2W (n = 59)
Week 16				
mNRI for HS-ABX, % (95% CI)	13.8 (NC, NC)	41.1 (26.7, 55.5)	46.1 (32.8, 59.4)	49.2 (NC, NC)
OC, n/N (%)	4/28 (14.3)	20/43 (46.5)	25/51 (49.0)	29/57 (50.9)
Week 48				
mNRI for HS-ABX, % (95% CI)	53.1 (34.1, 72.2)	42.4 (26.6, 58.3)	45.5 (31.6, 59.4)	52.2 (39.1, 65.4)
OC, n/N (%)	15/23 (65.2)	23/31 (74.2)	25/38 (65.8)	32/49 (65.3)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing lesion count assessment in the given week, and percentages are calculated accordingly.

ABX, antibiotics; CI, confidence interval; HS, hidradenitis suppurativa; IHS4, International Hidradenitis Suppurativa Severity Score System; IHS4-55, 55% reduction in IHS4 total score; mNRI, modified non-responder imputation; NC, not calculable; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks.

6. Proportion of patients with flare, at 16 weeks and 48 weeks in the pooled BE HEARD population biologic-experienced subgroup are presented in Table 14

Table 14 Proportion of patients with flare, at 16 weeks and 48 weeks in the pooled BE HEARD population biologic-experienced subgroup (mNRI for HS-ABX; OC)

Proportion with flare	Placebo/BKZ 320mg Q2W n=29	BKZ 320 mg Q4W/Q4W n = 47	BKZ 320 mg Q2W/Q4W n = 56	BKZ 320mg Q2W/Q2W
Week 16				
mNRI for HS-ABX, % (95% CI)	44.8 (NC, NC)	15.7 (5.0, 26.3)	16.5 (6.7, 26.3)	15.3 (NC, NC)
OC, n/N (%)	9/28 (32.1)	5/43 (11.6)	5/51 (9.8)	5/57 (8.8)
Week 48				
mNRI for HS-ABX, % (95% CI)	17.5 (3.6, 31.5)	36.1 (21.9, 50.4)	31.2 (18.8, 43.5)	20.0 (9.6, 30.5)
OC, n/N (%)	0/23	0/31	0/38	2/49 (4.1)

mNRI for HS-ABX: Patients who took systemic antibiotics as rescue medication for HS as defined by the principal investigator or who discontinued due to adverse event or lack of efficacy were treated as experiencing a flare at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing lesion count, and percentages are calculated accordingly.
ABX, antibiotics; BKZ, bimekizumab; CI, confidence interval; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; NC, not calculable; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks.

7. The following patient-reported outcome data are presented for the biologic-experienced subgroup (pooled BE HEARD trial population):
    a. Change from baseline to week 16 in worst skin pain NRS: Table 15
    b. HSSDD worst skin pain NRS response based on at least a 3-point decrease at week 16: Table 16
    c. HSSDD worst skin pain NRS response based on 30% reduction and at least 2 points reduction at week 16: Table 17
    d. HSSQ 0 skin pain responses among patients with baseline HSSQ ≥ 1: Table 18
    e. Mean change from baseline to week 16 in DLQI: Table 19
    f. DLQI MCID responses at week 16: Table 20
    g. HiSQOL total score and domain scores at baseline, and mean change from baseline to week 16 and week 48: Table 21
    h. EQ-5D-3L change from baseline to week 16 and week 48: Table 22

The HSSDD was completed daily from Screening through Week 16. Given that HSSDD was not measured in the maintenance period, data have been provided for placebo, bimekizumab 320 mg Q2W and bimekizumab Q4W up to week 16 (i.e. not further split by maintenance dosing regimen).

Table 15 Change from baseline to week 16 in worst skin pain NRS in the pooled BE HEARD population biologic-experienced subgroup (MI for HS-ABX)

Worst skin pain NRS, mean (SE)	PBO (n = 29)	BKZ 320 mg Q4W (n = 47)	BKZ 320 mg Q2W (n = 115)
Baseline	5.8 (0.5)	5.8 (0.4)	6.1 (0.2)
Change from baseline to week 16	−0.5 (0.4)	−1.4 (0.4)	−1.9 (0.3)

MI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as having experienced an intercurrent event. Intermittent 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 multiple imputation method for missing data.
ABX, antibiotics; BKZ, bimekizumab; CI, confidence interval; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 16 HSSDD worst skin pain NRS response based on at least a 3-point decrease at week 16 in pooled BE HEARD population biologic-experienced subgroup (mNRI for HS-ABX; OC)

Proportion with worst skin pain NRS response	PBO (n = 18)	BKZ 320 mg Q4W (n = 35)	BKZ 320 mg Q2W (n = 86)
mNRI for HS-ABX, % (95% CI)	8.2 (0.0, 22.7)	18.6 (4.0, 33.3)	31.8 (21.4, 42.2)
OC, n/N (%)	1/15 (6.7)	4/21 (19.0)	20/65 (30.8)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing assessment, and percentages are calculated accordingly.
Skin pain response was defined as at least a 3-point decrease from baseline in HSSDD weekly worst skin pain score among study participants with a score of ≥ 3 at baseline.
ABX, antibiotics; BKZ, bimekizumab; CI, confidence interval; HS, hidradenitis suppurativa; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary; mNRI, modified non-responder imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 17 HSSDD worst skin pain NRS response based on 30% reduction and at least 2-point reduction at week 16 in pooled BE HEARD population biologic-experienced subgroup (mNRI for HS-ABX; OC)

Proportion with worst skin pain NRS response	PBO (n = 18)	BKZ 320 mg Q4W (n = 35)	BKZ 320 mg Q2W (n = 86)
mNRI for HS-ABX, % (95% CI)	20.5 (0.3, 40.7)	40.8 (22.6, 59.0)	44.4 (33.3, 55.4)

OC, n/N (%)	4/15 (26.7)	10/21 (47.6)	29/65 (44.6)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing assessment in the given week, and percentages are calculated accordingly.
NRS30, a ≥ 30% reduction and reduction of ≥ 2 units from baseline in HSSDD weekly worst skin pain NRS score, assessed in patients with a baseline HSSDD score of ≥ 3.
ABX, antibiotics; CI, confidence interval; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; NRS, numerical rating scale; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 18 HSSQ 0 skin pain responses among patients with baseline HSSQ ≥ 1 in pooled BE HEARD population biologic-experienced subgroup (mNRI for HS-ABX; OC)

Proportion with HSSQ 0 response	PBO/BKZ 320 mg Q2W (n = 26)	BKZ 320 mg Q4W/Q4W (n = 47)	BKZ 320 mg Q2W/Q4W (n = 54)	BKZ 320 mg Q2W/Q2W (n = 59)
mNRI for HS-ABX analysis				
Week 16, % (95% CI)	0.0% (NC, NC)	6.9% (0.0–14.4%)	2.0% (0.0–5.8%)	6.8% (NC, NC)
Week 48, % (95% CI)	8.5% (0.0–19.8%)	7.4% (0.0–15.4%)	6.1% (0.0–12.9%)	12.8% (4.0–21.7%)
OC analysis				
Week 16, n/N (%)	0/25	3/43 (7.0%)	2/49 (4.1%)	4/57 (7.0%)
Week 48, n/N (%)	2/19 (10.5%)	5/31 (16.1%)	3/37 (8.1%)	7/49 (14.3%)

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.
OC: n/N denominator represents number of patients with a non-missing assessment in the given week, and percentages are calculated accordingly.
ABX, antibiotics; CI, confidence interval; HS, hidradenitis suppurativa; HSSQ, Hidradenitis Suppurativa Symptom Questionnaire; mNRI, modified non-responder imputation; OC, observed case; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 19 Change from baseline to week 16 in DLQI in pooled BE HEARD population biologic-experienced subgroup (MI for HS-ABX)

DLQI	PBO/BKZ 320 mg Q2W (n = 29)	BKZ 320 mg Q4W/Q4W (n = 47)	BKZ 320 mg Q2W/Q4W (n = 56)	BKZ 320 mg Q2W/Q2W (n = 59)
Baseline score, mean (SE)	14.2 (1.5)	13.6 (1.1)	12.5 (1.0)	13.2 (0.9)
Change from baseline, mean (SE)	−2.9 (1.3)	−6.0 (1.1)	−4.4 (0.8)	−5.0 (0.7)

MI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as having experienced an intercurrent event. Intermittent 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 multiple imputation method for missing data.
ABX, antibiotics; BKZ, bimekizumab; CI, confidence interval; DLQI, Dermatology Life Quality Index; HS, hidradenitis suppurativa; MCMC, Markov chain Monte Carlo imputation; MI, multiple imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.

Table 20 DLQI MCID responses at week 16 in pooled BE HEARD population biologic-experienced subgroup (mNRI for HS-ABX; OC)

Analysis	PBO/BKZ 320 mg Q2W (n = 24)	BKZ 320 mg Q4W/Q4W (n = 42)	BKZ 320 mg Q2W/Q4W (n = 47)	BKZ 320 mg Q2W/Q2W (n = 55)
mNRI for HS-ABX analysis				

DLQI MCID response, % (95% CI)	37.5 (NC–NC)	58.0 (42.8–73.2)	52.1 (37.5–66.6)	60.7 (47.7–73.7)
OC analysis				
DLQI MCID response, n/N (%)	10/23 (43.5%)	25/38 (65.8%)	24/42 (57.1%)	34/53 (64.2%)

DLQI MCID was defined as a ≥ 4-point reduction from baseline in DLQI total score in patients with baseline DLQI ≥ 4.

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.

OC: n/N denominator represents number of patients with a non-missing DLQI total score, and percentages are calculated accordingly.

BKZ, bimekizumab; MCID, minimal clinically important difference; mNRI, modified non-responder imputation; OC, observed case; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 21 HiSQOL total score and domain scores at baseline, and change from baseline to week 16 and week 48 in pooled BE HEARD population biologic-experienced subgroup (MI for HS-ABX)

HiSQOL domain (possible range)	Placebo/BKZ 320 mg Q2W (n = 29)			BKZ 320mg Q4W/Q4W (N=47)			BKZ 320mg Q2W/Q4W (N=56)			BKZ 320mg Q2W/Q2W (N=59)		
	Baseline	Week 16	Week 48	Baseline	Week 16	Week 48	Baseline	Week 16	Week 48	Baseline	Week 16	Week 48
Total Score (0–68)	28.7 (2.8)	−3.2 (2.5)	−12.8 (3.0)	30.1 (2.0)	−13.6 (2.3)	−15.8 (2.1)	27.2 (1.8)	-10.9 (1.7)	-12.8 (1.8)	28.2 (1.6)	-11.2 (1.6)	-15.3 (1.6)
Symptoms domain (0–16)	8.9 (0.7)	-0.9 (0.7)	-3.5 (0.8)	8.9 (0.5)	−2.8 (0.6)	−3.6 (0.7)	8.4 (0.5)	-2.7 (0.5)	-3.0 (0.6)	8.7 (0.4)	-2.4 (0.4)	-3.7 (0.5)
Psychosocial domain (0–20)	6.3 (0.8)	−0.4 (0.7)	−2.6 (0.9)	6.4 (0.7)	−3.3 (0.7)	−3.6 (0.7)	5.4 (0.5)	-1.9 (0.5)	-2.1 (0.6)	5.7 (0.5)	-2.3 (0.5)	-3.3 (0.5)
Activities-adaptation domain (0–32)	13.5 (1.6)	−2.2 (1.4)	−6.8 (1.7)	14.7 (1.1)	−7.4 (1.2)	−8.3 (1.1)	13.4 (1.0)	-6.3 (0.9)	-7.6 (0.9)	13.7 (0.8)	-6.4 (0.8)	-8.3 (0.9)

Data are mean (SE).

MI for HS-ABX: patients who discontinued study treatment due to lack of efficacy/adverse events, or who received systemic antibiotics identified as rescue medication for HS by the principal investigator, were set to missing and subsequently imputed using the MI method for missing data.

ABX, antibiotics; HS, hidradenitis suppurativa; HiSQOL, Hidradenitis Suppurativa Quality of Life; MI, multiple imputation; SE, standard error.

Table 22 EQ-5D-3L change from baseline to week 16 and week 48 in pooled BE HEARD population biologic-experienced subgroup (OC)

EQ-5D-3L	Placebo/ BKZ 320 mg Q2W (n = 29)	BKZ 320 mg Q4W/Q4W (n = 47)	BKZ 320 mg Q2W/Q4W (n = 56)	BKZ 320 mg Q2W/Q2W (n = 59)
Baseline				
Visit N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16				
Visit N; change from baseline N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48				
Visit N; change from baseline N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

OC, observed case; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation.

8. The number of patients discontinuing and primary reasons for study discontinuation are presented for the biologic-experienced subgroup (pooled BE HEARD trial population) in Table 23.

Table 23 Discontinuation in the pooled BE HEARD population biologic-experienced subgroup

Primary reason for discontinuation	Placebo/ BKZ 320 mg Q2W (n = 29)	BKZ 320 mg Q4W/Q4W (n = 47)	BKZ 320 mg Q2W/Q4W (n = 56)	BKZ 320 mg Q2W/Q2W (n = 59)
Discontinued study				
n (%)	6 (20.7)	16 (34.0)	18 (32.1)	10 (16.9)
Primary reason for study discontinuation				
Adverse event	1 (3.4)	2 (4.3)	4 (7.1)	1 (1.7)
Lack of efficacy	1 (3.4)	4 (8.5)	3 (5.4)	1 (1.7)
Protocol violation	1 (3.4)	0	2 (3.6)	1 (1.7)
Lost to follow-up	0	1 (2.1)	1 (1.8)	1 (1.7)
Consent withdrawn	3 (10.3)	8 (17.0)	8 (14.3)	6 (10.2)
Other	0	1 (2.1)	0	0

A17. PRIORITY: Please clarify whether patients given antibiotics (whether as rescue treatment or not) continued to be followed up and have outcomes measured, and how this impacts the distinction between "All ABX", "HR ABX" and "OC" analyses. In particular, please provide a table or data to clarify for both BE HEARD trials and for each trial arm:

a) Total numbers of patients with missing HiSCR outcome data (for any reason) at 16 and 48 weeks

Table 24 Missing HiSCR outcome data BE HEARD I and II (RS)

	BE HEARD I				BE HEARD II			
Missing HiSCR outcome data	PBO/BKZ 320mg Q2W N=72	BKZ 320mg Q4W/Q4W N=144	BKZ 320mg Q2W/Q4W N=146	BKZ 320mg Q2W/Q2W N=143	PBO/BKZ 320mg Q2W N=74	BKZ 320mg Q4W/Q4W N=144	BKZ 320mg Q2W/Q4W N=146	BKZ 320mg Q2W/Q2W N=145
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

RS, Randomised set.

The percentages in the above table were calculated by subtracting the number of participants with a non-missing lesion count assessment at the given week from 100%, and percentages are calculated accordingly. Missingness can be attributed to any reason (discontinuation prior to the visit in question, missed visit etc.). In the primary efficacy analyses, these missing data would be imputed as non-response if an intercurrent event occurred before this timepoint. If missing but no intercurrent event, these missing data would be imputed and contribute to the determination of response level. A breakdown of the observed data, intercurrent events, and missing data that is imputed for week 16 HiSCR50 outcome (ALL-ABX) is shown in Table 25.

b) **Numbers of patients included in "OC" analyses but not in "All ABX" and "HR ABX" analyses**

Table 25. Number of patients with HiSCR50 data observed or imputed at week 16 in BE HEARD I and BE HEARD II (RS)

	BE HEARD I			BE HEARD II		
n(%)	PBO (N=72)	BKZ Q2W (N=289)	BKZ Q4W (N=144)	PBO N=74)	BKZ Q2W (N=291)	BKZ Q4W (N=144)
OC	51 (70.8%)	214 (74.0%)	102 (70.8%)	64 (86.5%)	225 (77.3%)	116 (80.6%)
NRI – All systemic antibiotic use	15 (20.8%)	47 (16.3%)	22 (15.3%)	6 (8.1%)	45 (15.5%)	18 (12.5%)
NRI – Discontinued due to adverse event	1 (1.4%)	5 (1.7%)	6 (4.2%)	1 (1.4%)	8 (2.7%)	1 (0.7%)
NRI – Discontinued due to loss of efficacy	0	0	0	0	0	0
MI	5 (6.9%)	23 (8.0%)	14 (9.7%)	3 (4.1%)	13 (4.5%)	9 (6.3%)

Randomised set. HiSCR: Hidradenitis Suppurativa Clinical Response; HiSCR50: ≥50% reduction from baseline in the total abscess and inflammatory nodule count with no 318 increase from baseline in abscess or draining tunnel count; MI: multiple imputation; mNRI: modified non-responder imputation; NRI: non-responder imputation; 319 OC: observed case; Q2W: every 2 weeks; Q4W: every 4 weeks.

Table 25 gives a detailed breakdown for the week 16 HiSCR50 outcome under the ALL-ABX method of intercurrent event handling. The observed patients not preceded by an intercurrent event are shown in the OC row. Those with missing data not preceded by an intercurrent event are shown in the MI row. These methodologies refer to data handling strategies, not patient care during the trial. Note that all patients with observed data contribute to both the "All ABX" and "HS ABX" analyses. However, if a patient has experienced an intercurrent event the observed data will be considered a non-response at that timepoint and all future timepoints. All patients observed or not are considered in both the All-ABX and HS-ABX analyses. The analyses differ in the definition of the systemic antibiotics considered as an intercurrent event only. The more stringent All-ABX analyses will consider more patients as non-responders due to intercurrent event status (whether they were responders or not) than the HS-ABX analysis. In both the All-ABX and HS-ABX scenarios missing data for patients who did not experience an intercurrent event are imputed using multiple imputation methodology.

c) **If patients were not followed up after antibiotic use, please supply a justification for this decision.**

Patients were followed up after antibiotic use (irrespective of whether this antibiotic use was considered an intercurrent event or not). For patients with antibiotic use constituting an intercurrent event, data collected following the intercurrent event was included in observed case analysis, but not in mNRI analyses (where the patient was considered to be a non-responder following the intercurrent event, irrespective of their observed data).

A18. Please explain the large difference in results between the mNRI (HS-ABX) analysis and the OC analysis in Figure 13 and the apparent difference in results between Table 24 and Figure 13.

In Figure 13, the percentages are higher for mNRI (HS-ABX) because subjects experiencing an intercurrent event were treated as having experienced a flare at all visits following the intercurrent event, irrespective of whether they were observed to experience a flare or not. These intercurrent events can only accumulate over time, increasing the number of patients deemed having a "flare" as the intercurrent event

affects the response status at the visit following the intercurrent event and all subsequent visits.

The difference between Figure 13 and Table 24 is that Figure 13 looks at the occurrence of flares on a visit-by-visit basis (i.e., assesses whether a patient experiences a flare at the given visit, rather than at any point up to that visit), whereas Table 24 looks at the cumulative occurrence/proportion of patients who have experienced a flare at any point during the period of interest.

A19. In the CS it is stated that there are no sub-group differences in effect for systemic antibiotic use, weight, Hurley score and race. Please explain how this decision was reached, as our inspection of the sub-group data suggests possible effects for each of these variables.

As a part of the integrated summary of efficacy of the pooled BE HEARD I and BE HEARD II studies, pre-specified subgroups were assessed for differences in efficacy. Response rates (HS-ABX) and confidence intervals (CIs) were calculated using logistic regression. Interaction nominal p-values were based on logistic regression with factors for treatment, Hurley stage at Baseline, feeder study, subgroup, and subgroup by treatment interaction. For HiSCR50 and HiSCR75 outcomes at week 16 nominal interaction p-values were not significant (or not calculable due to small sample size) for BKZ Q2W or BKZ Q4W vs. placebo in any subgroup. Although some differences in efficacy were observed visually, especially in subgroups with low patient numbers (e.g., systemic antibiotic use at baseline, black race), these results should be interpreted with caution. In publications, subgroup analysis was exploratory and no formal analysis performed. Regardless of subgroup, BKZ demonstrated consistent and clinically meaningful efficacy.

A20. How do the characteristics of the UK target population (in particular systemic antibiotic use, weight, Hurley score and race) compare to the characteristics of those in the trials?

The UK population varies considerably in different geographic regions in relation to disease demographics. Therefore, some localities will match the patient demographics given in the trials and some localities will not. However, UK prescribing decisions are based on disease severity, not characteristics such as antibiotic use or race, although in current UK practice there is a greater use of

systemic antibiotics. Given the low number of therapies available and our gaps in understanding of the disease, current prescribing practices do not adopt a 'precision medicine approach'. Therefore, the principal target demographic of bimekizumab is moderate-to-severe HS.

NMA

A21. PRIORITY: Please supply NMAs for IHS4-55, IHS4 change, DT count, skin pain response and a quality-of-life outcome, using only the biologic-experienced subpopulation (as in Section B.2.9.2.3 for HiSCR).

Analysis of the biologic-experienced population was undertaken by UCB informed by data from Zouboulis 2024 [6] and Zouboulis 2023a [22] using the same methodology as that in the CS but utilised 50,000 burn-in and 50,000 simulations and was conducted using an NMA Engine adapted from the MetaInsight app (https://crsu.shinyapps.io/MetaInsight/) for UCB use [11]. Biologic experienced outcomes are only available for secukinumab and bimekizumab phase 3 studies, including SUNRISE/SUNSHINE (pooled) and BE HEARD I/II. BE HEARD I/II outcomes were pooled to align with the presentation of the pooled SUNRISE/SUNSHINE outcomes. Both fixed-effect and random-effects models were tested. When considering all outcomes, DIC was lowest for the fixed-effect model or the difference was less than 5 across all models. Given the sparse number of trials in the network and DIC results, the fixed-effect model was preferred.

The results of the NMAs assessing HiSCR75, IHS4-55, reduction in worst skin pain as measured using NRS30, flare, DLQI MCID 5-point reduction and EQ5D VAS in the biologic-experienced population are shown in Table 1. Note that outcome data were not available for DT count or IHS4 change in this population so are not included.

The NMA results show that patients treated with bimekizumab 320 mg Q2W had higher odds of achieving response thresholds in HiSCR75 and IHS4-55 compared to all other active treatments and placebo at week 16.

Overall, the analyses in biologic-experienced patients show similar or numerically better point estimates for bimekizumab 320 mg Q2W when compared to the overall population. However, given the increased uncertainty in the biologic-experienced

NMAs due to the limited number of trials in each network and small trial sample sizes, UCB believe it is more appropriate for the larger overall mixed population to be used in the appraisal for decision making, as was adopted in TA935 [7].

Table 25 Week 16 NMA outcomes among biologic-experienced patients (fixed-effect model)

BKZ Q2W vs	Binary: OR (95% CrI) / Continuous: MD (95% CrI)							
	HiSCR75 (OC)	HiSCR75 (NRI)	IHS4-55 (OC)	IHS4-55 (NRI)	Flare (mNRI HS-ABX)	Reduction in worst skin pain (NRS30) (mNRI HS-ABX)	DLQI MCID 5-point reduction (OC)	EQ5D VAS (OC)
PBO	**4.07 (1.43, 15.10)**	**3.87 (1.36, 14.60)**	**6.43 (2.22, 24.10**	**5.84 (2.08, 21.60)**	**0.27 (0.11, 0.63)**	2.97 (0.95, 11.55)	2.03 (0.78, 5.53)	5.93 (-2.74, 14.57)
BKZ QW4	1.20 (0.58, 2.57)	1.24 (0.60, 2.61)	1.15 (0.57, 2.36)	1.20 (0.60, 2.41)	1.10 (0.48, 2.60)	1.19 (0.54, 2.70)	0.74 (0.34, 1.58)	-2.62 (-8.96, 3.75)
SEC Q4W	2.41 (0.61, 11.20)	1.93 (0.48, 9.07)	**4.01 (1.11, 17.8)**	3.56 (1.00, 15.20)	**0.29 (0.10, 0.88)**	0.73 (0.16, 3.65)	0.95 (0.29, 3.23)	1.15 (-9.85, 12.06)
SEC Q2W	2.53 (0.63, 11.70)	2.06 (0.52, 9.77)	**4.67 (1.27, 20.6)**	**4.20 (1.18, 18.2)**	**0.29 (0.09, 0.87)**	0.76 (0.17, 3.76)	1.21 (0.37, 4.14)	-0.07 (-11.17, 11.07)

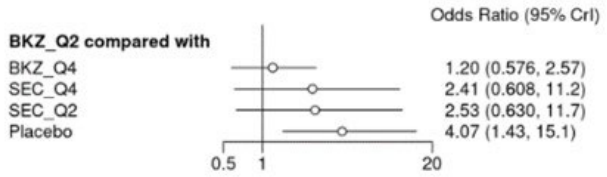
Statistically significant results are highlighted in **bold**.

mNRI for HS-ABX: patients who took any systemic antibiotic as HS rescue medication or who discontinued treatment due to AEs or lack of efficacy are treated as non-responders at all subsequent visits.

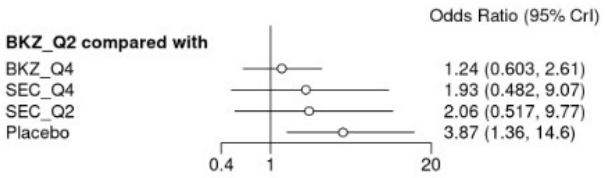
ABX, antibiotics; BKZ, bimekizumab; CrI, credible interval; DLQI MCID Dermatology Life Quality Index minimal clinically important difference (reduction of ≥ 5 units from baseline in DLQI, assessed in patients with a baseline DLQI score of ≥ 5); EQ5DVAS 5-dimension, 3-level EuroQol questionnaire visual analogue scale; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; NRI non-responder imputation; NRS30 numerical rating scale (≥ 30% reduction and reduction of ≥ 2 units from baseline in HSSDD weekly worst skin pain NRS score, assessed in patients with a baseline NRS score of ≥ 3); MD, mean difference; OC, observed cases; OR, odds ratio; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab.

Figure 4. Forest plots of week 16 NMA results: bimekizumab 320 mg Q2W vs other treatments (fixed-effect model)

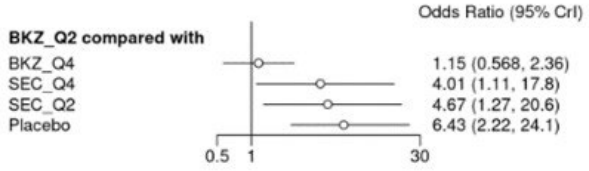
HiSCR75 (OC)



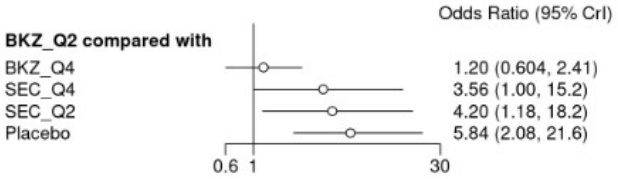
HiSCR75 (NRI)



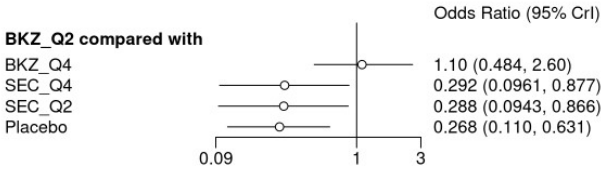
IHS4-55 (OC)



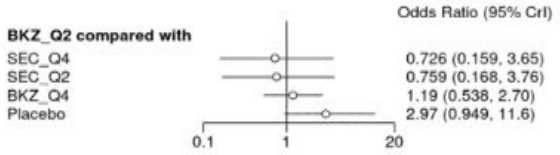
IHS4-55 (NRI)



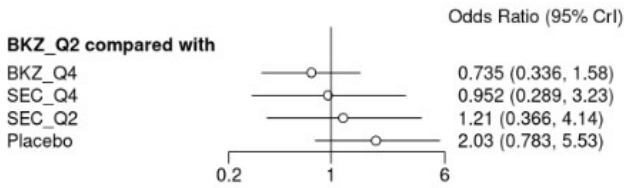
Flare (mNRI HS-ABX)



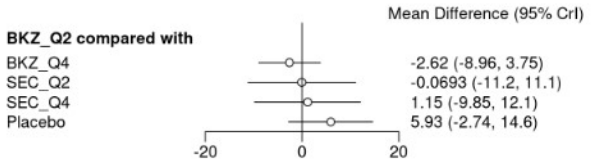
Reduction in worst skin pain (NRS30) (mNRI HS-ABX)



DLQI MCID 5-point reduction (OC)



EQ5D VAS (OC)



A22. PRIORITY: Please present additional baseline characteristics for studies included in the NMA, i.e., number (and proportion) of Black patients (in addition to White and Asian patients) and the other baseline characteristics presented in Table 11 for the BE HEARD trials, where available. Please also provide a separate table of baseline characteristics for the biologic-experienced subgroup of each study included in the NMA, where available.

Please find below baseline characteristic data as requested.

Table 26 Baseline characteristics for studies included in the NMA

Category	HS0001			PIONEER I		PIONEER II		NCT00918255		SHARPS		SUNSHINE			SUNRISE		
	PBO	BKZ Q2W	ADA QW	PBO	ADA QW	PBO	ADA QW	PBO	ADA (QW)	PBO	ADA	PBO	SEC, Q2W	SEC, Q4W	PBO	SEC Q2W	SEC Q4W
N	21	46	21	154	153	163	163	51	51	103	103	180	181	180	180	181	180
Study participant characteristics																	
Age, years, mean ± SD	40.7 ±12.8	37.4 ±11.9	31.1 ±9.4	37.8 ±11.3	36.2 ±10.8	36.1 ±12.2	34.9 ±10.0	37.8 ±12.1	35.1 ±10.7	36.8 ±10.8	38.5 ±11.7	35.5 ±10.8	37.1 ±12.5	35.7 ±11.7	36.2 ±11.3	37.3 ±11.5	35.5 ±11.4
Gender, n (%)																	
Male	7 (33.0)	16 (34.8)	4 (19.0)	49† (31.8)	62† (40.5)	50† (30.7)	55† (33.7)	15 (29.4)	15 (29.4)	48 (47)	52 (50)	78 (43)	79 (44)	80 (44)	78 (43)	82 (46)	77 (43)
Female	14 (67.0)	30 (65.2)	17 (81.0)	105 (68.2)	91 (59.5)	113 (69.3)	108 (66.3)	36 (70.6)	36 (70.6)	55 (53)	51 (50)	102 (57)	102 (56)	100 (56)	105 (57)	98 (54)	103 (57)
Body weight, kg, mean ± SD	94.8 (18.7)	97.7 (24.2)	100.2 (23.8)	99.3 ±25.13	97.1 ±24.90	95.7 ±25.87	90.2 ±21.74	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
≤ 100 kg, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
> 100 kg, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
BMI, kg/m^2, mean ± SD	33.2 ±5.8	34.5 ±8.2	36.9 ±10.6	34.5 ±7.9	33.0 ±7.6	32.9 ±7.9	31.3 ±7.4	NR	NR	31.7 ±7.1	32.6 ±7.1	32.0 ±7.1	32.6 ±7.9	32.8 ±7.9	31.4 ±7.4	31.9 ±7.8	32.0 ±7.5
Smoking status, n (%)																	
Never	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Current	NR	NR	NR	92 (59.7)	81 (52.9)	109 (67.3)	105 (64.4)	NR	NR	70 (69.0)	69 (68.0)	101 (56)	95 (53)	96 (53)	106 (58)	97 (54)	90 (50)
Former	NR	NR	NR	NR	NR	NR	NR	29 (56.9)	30 (58.8)	NR	NR	30 (17)	26 (14)	28 (16)	24 (13)	32 (18)	25 (14)
Racial group, n (%)																	
White	12 (57.1)	35 (76.1)	14 (66.7)	118 (76.6)	116 (75.8)	130 (79.8)	143 (87.7)	37 (72.5)	37 (72.5)	97 (95.0)	96 (93.0)	139 (77)	145 (80)	146 (81)	143 (78)	133 (74)	139 (77)
Black	6 (28.6)	10 (21.7)	4 (19.0)	29 (18.8)	33 (21.6)	20 (12.3)	9 (5.5)	8 (15.7)	9 (17.6)	4 (4.0)	4 (4.0)	12 (7)	15 (8)	10 (6)	12 (7)	18 (10)	19 (11)
Asian	1 (4.8)	0 (0)	3 (14.3)	4 (1.3)		10 (3.1)		NR	NR	NR	NR	24 (13)	19 (11)	23 (13)	19 (10)	16 (9)	16 (9)
Geographical region, n (%)																	

Category	HS0001			PIONEER I		PIONEER II		NCT00918255		SHARPS		SUNSHINE			SUNRISE		
	PBO	BKZ Q2W	ADA QW	PBO	ADA QW	PBO	ADA QW	PBO	ADA (QW)	PBO	ADA	PBO	SEC, Q2W	SEC, Q4W	PBO	SEC Q2W	SEC Q4W
N	21	46	21	154	153	163	163	51	51	103	103	180	181	180	180	181	180
North America	13 (61.9)	21 (45.7)	10 (47.6)	NR	NR	NR	NR	36 (70.6)	41 (80.4)	NR	NR	NR	NR	NR	NR	NR	NR
Central/Eastern Europe	3 (14.3)	5 (10.9)	3 (14.3)	NR	NR	NR	NR	15 (29.4)	10 (19.6)	NR	NR	NR	NR	NR	NR	NR	NR
Western Europe	2 (9.5)	9 (19.6)	3 (14.3)	NR	NR	NR	NR			NR	NR	NR	NR	NR	NR	NR	NR
Asia/Australia	3 (14.3)	11 (23.9)	5 (23.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baseline disease characteristics																	
Duration of disease, years, Mean ± SD	9.5 ±8.4	9.0 ±8.8	8.6 ±5.7	9.4 [1.0, 43.0]‡	8.8 [1.1, 40.4]‡	9.9 [1.2, 68.5]‡	9.0 [1.0, 43.5]‡	13.4 ±10.4	11.3 ±9.1	10.0 ±9.0	11.7 ±10.5	7.5 ±7.0	7.4 ±8.0	6.6 ±6.7	7.0 ±6.7	7.1 ±7.0	8.2 ±8.4
Hurley stage (derived), n (%)																	
II	10 (47.6)	23 (50.0)	10 (47.6)	81 (52.6)	80 (52.3)	89 (54.6)	86 (52.8)	29 (56.9)	28 (54.9)	54 (52.0)	53 (51.0)	121 (67)	104 (58)	107 (59)	110 (60)	92 (51)	106 (59)
III	11 (52.4)	23 (50.0)	11 (52.4)	73 (47.4)	73 (47.7)	74 (45.4)	77 (47.2)	15 (29.4)	15 (29.4)	49 (48.0)	50 (49.0)	51 (28)	70 (39)	63 (35)	70 (38)	82 (46)	68 (38)
AN count, mean ± SD	22.1 (21.2)	14.5 (11.9)	20.0 (11.5)	14.4 ±14.8	14.3 ±11.9	11.9 ±11.0	10.7 ±8.1	NR	NR	11.3 ±12.6	10.3 ±7.5	12.8 ±8.2	12.9 ±9.6	12.6 ±8.4	12.8 ±8.5	13.9 ±9.9	13.3 ±8.8
Hurley stage II	24.8 (29.0)	14.1 (11.5)	15.9 (10.2)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hurley stage III	19.7 (11.1)	15.0 (12.6)	23.7 (11.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
DT count, mean ± SD	5.5 (5.3)	5.3 (5.1)	4.4 (4.1)	3.8 ±4.4	4.6 ±5.2	3.7 ±5.2	3.0 ±4.1	3.4 ±NR	5.6 ±NR	4.0 ±5.4	3.6 ±4.0	2.4 ±3.2	2.9 ±3.4	2.5 ±3.5	2.6 ±3.2	3.0 ±3.6	2.5 ±3.5
Hurley stage II	3.2 (4.2)	2.7 (3.2)	2.4 (2.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hurley stage III	7.5 (5.5)	8.0 (5.3)	6.3 (4.6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
IHS4 score, mean ± SD	49.8 ±34.7	40.5 ±29.8	42.0 ±26.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
HiSQOL total score, mean ± SD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Symptom score	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Psychosocial score	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Activities and adaptations score	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
DLQI total score, mean ± SD	12.7 ±5.7	11.7 ±8.0	14.5 ±7.9	16.0 ±7.1	16.3 ±6.6	14.9 ±7.3	14.1 ±7.7	15.4 ±7.7	16.4 ±7.5	12.9 ±7.1	13.6 ±7.3	13.8 ±7.2	14.2 ±6.7	13.4 ±6.2	14.5 ±6.9	15.7 ±7.1	14.6 ±7.2
HSSDD worst pain score, mean ± SD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Category	HS0001			PIONEER I		PIONEER II		NCT00918255		SHARPS		SUNSHINE			SUNRISE		
	PBO	BKZ Q2W	ADA QW	PBO	ADA QW	PBO	ADA QW	PBO	ADA (QW)	PBO	ADA	PBO	SEC, Q2W	SEC, Q4W	PBO	SEC Q2W	SEC Q4W
N	21	46	21	154	153	163	163	51	51	103	103	180	181	180	180	181	180
Antibiotic use, n (%)																	
Yes	3 (14.3)	4 (8.7)	4 (19.0)	NR	NR	32[¶] (NR)	31[¶] (NR)	NR	NR	NR	NR	150 (83.3)	146 (80.7)	149 (82.8)	151 (82.5)	151 (83.9)	152 (84.4)
No	18 (85.7)	42 (91.3)	17 (81.0)	NR	NR	131[¶] (NR)	132[¶] (NR)	NR	NR	NR	NR	30 (16.7)	35 (19.3)	31 (17.2)	32 (17.5)	29 (16.1)	28 (15.6)
Prior biologic use for HS, n (%)																	
Yes	0[§]	0[§]	0[§]	0[§]	0[§]	0[§]	0[§]	NR	NR	NR	NR	46 (25.6)	44 (24.3)	39 (21.7)	48 (26.2)	36 (20.0)	42 (23.3)
No	21 (100)	46 (100)	21 (100)	154 (100)	153 (100)	163 (100)	163 (100)	NR	NR	NR	NR	134 (74.4)	137 (75.7)	141 (78.3)	135 (73.8)	144 (80.0)	138 (76.7)

[†]Calculated from number and % female; [‡]Median [range]; [¶]Antibiotics at baseline; [§]Patients were eligible if they had not received prior TNFα inhibitor treatment

Abbreviations: ADA, adalimumab; BKZ, bimekizumab; BMI, body mass index; HS, Hidradenitis Suppurativa; IHS4, International Hidradenitis Suppurativa Severity Score System; QW/Q2W/Q4W, once weekly/every 2 weeks/every 4 weeks; SD, standard deviation; SEC, secukinumab.

Table 27 Baseline characteristics for biologic-experienced subgroups in studies included in the NMA

Category	BE HEARD I			BE HEARD II			SUNSHINE + SUNRISE		
	PBO	BKZ Q4W	BKZ Q2W	PBO	BKZ Q4W	BKZ Q2W	PBO	SEC Q2W	SEC Q4W
N	19	31	75	10	16	40	94	80	81
Study participant characteristics									
Age, years, mean ± SD	37.9 ± 12.1	36.7 ± 10.6	38.4 ± 13.4	42.5 ± 12.2	36.4 ± 10.2	38.9 ± 13.3	37.8 ± 11.6	40.3 ± 12.9	38.7 ± 12.1
Gender, n (%)									
Male	4 (21.1)	14 (45.2)	35 (46.7)	4 (40.0)	5 (31.3)	23 (57.5)	37 (39.4)	36 (45.0)	35 (43.2)
Female	15 (78.9)	17 (54.8)	40 (53.3)	6 (60.0)	11 (68.8)	17 (42.5)	57 (60.6)	44 (55.0)	46 (56.8)
Body weight, kg, mean ± SD	90.6 ± 26.6	105.8 ± 25.1	95.3 ± 26.7	100.5 ± 27.9	98.2 ± 21.1	99.4 ± 26.2	92.2 ± 21.8	95.9 ± 24.5	95.8 ± 23.8
≤ 100 kg, n (%)	13 (68.4)	14 (45.2)	47 (62.7)	6 (60.0)	9 (56.3)	22 (55.0)	NR	NR	NR
> 100 kg, n (%)	6 (31.6)	17 (54.8)	28 (37.3)	4 (40.0)	7 (43.8)	18 (45.0)	NR	NR	NR
BMI, kg/m^2, mean ± SD	31.64 ± 7.33	35.80 ± 8.36	31.86 ± 7.99	34.70 ± 10.93	34.56 ± 6.53	32.58 ± 7.96	31.6 ± 6.9	32.5 ± 7.6	32.8 ± 8.2
Smoking status, n (%)									
Never	7 (36.8)	11 (35.5)	22 (29.3)	4 (40.0)	5 (31.3)	10 (25.0)	27 (28.7)	18 (22.5)	29 (35.8)
Current	12 (63.2)	11 (35.5)	38 (50.7)	6 (60.0)	5 (31.3)	19 (47.5)	52 (55.3)	45 (56.3)	40 (49.4)
Former	0 (0)	9 (29.0)	15 (20.0)	0 (0)	6 (37.5)	11 (27.5)	15 (16.0)	17 (21.3)	12 (14.8)
Racial group, n (%)									
White	16 (84.2)	25 (80.6)	67 (89.3)	7 (70.0)	11 (68.8)	32 (80.0)	77 (81.9)	66 (82.5)	67 (82.7)
Black	2 (10.5)	1 (3.2)	3 (4.0)	2 (20.0)	2 (12.5)	3 (7.5)	8 (8.5)	8 (10.0)	11 (13.6)
Asian	0 (0)	1 (3.2)	0 (0)	1 (10.0)	1 (6.3)	2 (5.0)	6 (6.4)	1 (1.3)	2 (2.5)
Geographical region, n (%)									
North America	6 (31.6)	8 (25.8)	19 (25.3)	5 (50.0)	9 (56.3)	12 (30.0)	NR	NR	NR
Central/Eastern Europe	4 (21.2)	7 (22.6)	21 (28.0)	2 (20.0)	1 (6.3)	6 (15.0)	NR	NR	NR
Western Europe	9 (47.4)	15 (48.4)	30 (40.0)	2 (20.0)	5 (31.3)	20 (50.0)	NR	NR	NR
Asia/Australia	0 (0)	1 (3.2)	5 (6.7)	1 (10.0)	1 (6.3)	2 (5.0)	NR	NR	NR
Baseline disease characteristics									
Duration of disease, years, Mean ± SD	12.7 ± 9.79	9.74 ± 8.72	8.33 ± 7.03	7.60 ± 4.24	9.24 ± 6.62	9.64 ± 9.07	9.4 ± 7.0	9.5 ± 8.4	9.2 ± 8.4
Hurley stage, n (%)									
II	9 (47.4)†	10 (32.3)†	20 (26.7)†	2 (20.0)	8 (50.0)	22 (55.0)	46 (48.9)	33 (41.3)	43 (53.1)
III	10 (52.6)†	21 (67.7)†	55 (73.3)†	8 (80.0)	8 (50.0)	18 (45.0)	47 (50.0)	47 (58.8)	38 (46.9)
AN count, mean ± SD	14.16 (9.31)	24.45 (47.39)	16.68 (13.34)	1	12.8 (SE 2.1)	16.5 (SE 2.2)	15.5 ± 9.8	15.1 ± 11.1	15.7 ± 11.3
Hurley stage II	15.11 ± 11.12 (n=9)	38.50 ± 82.67 (n=10)	12.10 ± 6.92 (n=20)	22.50 ± 10.61	8.63 ± 2.83	12.59 ± 7.21	NR	NR	NR
Hurley stage III	13.30 ± 7.85 (n=10)	17.76 ± 12.15 (n=21)	18.35 ± 14.71 (n=55)	17.50 ± 6.46	16.88 ± 10.02	21.28 ± 18.48	NR	NR	NR
DT count, mean ± SD	3.84 (5.09)	5.90 (6.00)	6.81 (6.16)	NR	NR	NR	3.0 ± 3.3	4.2 ± 3.8	4.2 ± 4.8
Hurley stage II	1.22 ± 1.92 (n=9)	0.90 ± 1.91 (n=10)	2.15 ± 3.17 (n=20)	2.50 ± 3.54	2.25 ± 2.12	2.23 ± 2.52	NR	NR	NR
Hurley stage III	6.20 ± 5.96 (n=10)	8.29 ± 5.82 (n=21)	8.51 ± 6.12 (n=55)	9.13 ± 5.77	3.00 ± 3.12	6.22 ± 4.40	NR	NR	NR
IHS4 score, mean ± SD	32.8 ± 23.9	53.6 ± 56.3	49.3 ± 37.4	53.3 ± 24.4	27.3 ± 15.5	35.7 ± 27.0	31.9 ± 21.1	36.4 ± 25.1	36.2 ± 26.0

Category	BE HEARD I			BE HEARD II			SUNSHINE + SUNRISE		
	PBO	BKZ Q4W	BKZ Q2W	PBO	BKZ Q4W	BKZ Q2W	PBO	SEC Q2W	SEC Q4W
N	19	31	75	10	16	40	94	80	81
HiSQOL total score, mean ± SD	26.16 ± 14.69	32.61 ± 13.75	28.65 ± 12.63 (n=74)	33.33 ± 15.87 (n=9)	25.13 ± 12.01	26.28 ± 12.44 (n=39)	NR	NR	NR
Symptom score	8.63 ± 3.59	9.45 ± 3.32	8.93 ± 3.37	9.33 ± 3.84 (n=9)	7.88 ± 2.78	7.92 ± 3.51 (n=39)	NR	NR	NR
Psychosocial score	5.05 ± 4.03	6.94 ± 4.76	5.59 ± 3.99	8.67 ± 4.80 (n=9)	5.44 ± 4.27	5.69 ± 4.10 (n=39)	NR	NR	NR
Activities and adaptations score	12.47 ± 8.41	16.23 ± 7.70	14.12 ± 6.66	15.33 ± 9.01 (n=9)	11.81 ± 6.91	12.67 ± 6.92 (n=39)	NR	NR	NR
DLQI total score, mean ± SD	13.2 ± 8.4	14.4 ± 7.7	13.3 ± 6.6	14.6 ± 7.8	11.9 ± 7.2	12.5 ± 7.3	15.1 ± 6.9 (n=86)	16.8 ± 6.5 (n=68)	16.4 ± 6.7 (n=71)
HSSDD worst pain score, mean ± SD	6.25 ± 2.71 (n=14)	5.93 ± 2.25 (n=27)	6.44 ± 2.26 (n=60)	5.07 ± 2.32 (n=8)	5.80 ± 2.89 (n=13)	5.67 ± 2.37 (n=36)	NR	NR	NR
Antibiotic use, n (%)									
Yes	2 (10.5)‡	2 (6.5)‡	3 (4.0)‡	1 (10.0)‡	1 (6.3)‡	5 (12.5)‡	85 (90.4)	66 (82.5)	73 (90.1)
No	17 (89.5)‡	29 (93.5)‡	72 (96.0)‡	9 (90.0)‡	15 (93.8)‡	35 (87.5)‡	9 (9.6)	14 (17.5)	8 (9.9)
Prior biologic use for HS, n (%)									
Yes	19 (100)	31 (100)	75 (100)	10 (100)	16 (100)	40 (100)	94 (100)	80 (100)	81 (100)
No	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

†Derived Hurley stage for each participant was the worst overall Hurley stage derived from the Hurley Stages recorded across all anatomical regions; ‡Derived antibiotic use at baseline was defined as eCRF record of a stable dose and regimen of systemic antibiotic use for at least 28 days prior to baseline; otherwise, derived antibiotic use at baseline was defined as “No”.

Abbreviations: ADA, adalimumab; BKZ, bimekizumab; BMI, body mass index; HS, Hidradenitis Suppurativa; IHS4, International Hidradenitis Suppurativa Severity Score System; QW/Q2W/Q4W, once weekly/every 2 weeks/every 4 weeks; SD, standard deviation; SE, standard error; SEC, secukinumab.

A23. PRIORITY: Baseline characteristics were similar across trials and comparisons for age and BMI, but there appeared to be quite large differences for potential outcome modifiers such as race and severity [Table 89, Appendices]. In addition, the trials involving adalimumab had patients with no prior biologic experience, in contrast to the other trials, that had around 20% of patients with previous biologic experience. Such clinical heterogeneity may have threatened the transitivity assumption. There is no evidence that the company have investigated possible inconsistency in the network. Please clarify how inconsistency was investigated.

From the BKZ trials, there was some evidence of race, severity and prior biologic experience acting as prognostic factors. However, the evidence was insufficient to suggest effect modification and, therefore, the potential differences in these characteristics across trials are unlikely to have a significant impact on the treatment comparisons in the NMA.

For the specific example of HiSCR50 responder rate differences, there was extensive overlap between 95% confidence intervals (CI) in the subgroups for BE HEARD I (Figure 5) and BE HEARD II (Figure 6).

Figure 5 **Selected subgroup analyses of HiSCR50 and responder rate differences: BE HEARD I trial (from CSR)(confidential)**

BKZ, bimekizumab; BMI, body mass index; CI, confidence interval; CSR, clinical study report; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, Hidradenitis Suppurativa; Q2W, every 2 weeks.

Figure 6 **Selected subgroup analyses of HiSCR50 and responder rate differences: BE HEARD II trial (from CSR)(confidential)**

BKZ, bimekizumab; BMI, body mass index; CI, confidence interval; CSR, clinical study report; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, Hidradenitis Suppurativa; Q2W, every 2 weeks.

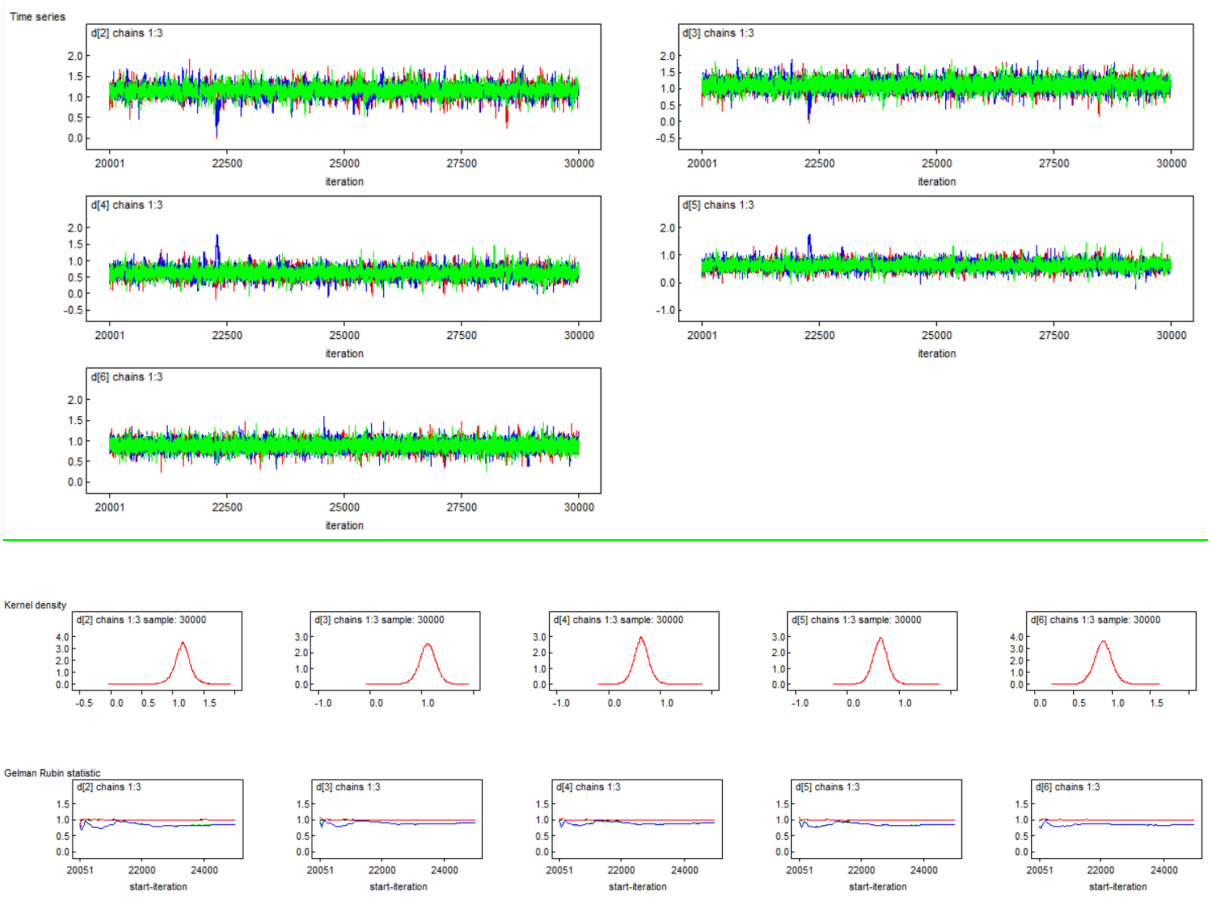
With respect to possible inconsistency in the treatment network, only one loop was identified, this was comprised of BKZ Q2W, ADA 40 mg QW and PBO. The ADA 40 mg QW vs PBO network edge was informed by four studies with two arms (PIONEER I/II; SHARPS; NCT00918255); the BKZ 320 mg Q2W was informed by

two studies with two arms (BE HEARD I/II); and one three-arm study (HS0001) informed all sides of the treatment loop. HS0001 was the only study informing the BKZ vs ADA edge. Given the limited timeframe and that ADA is not considered within scope in the company submission, other analyses were prioritised over this assessment of inconsistency.

A24. The minimum length of burn-in (20,000 iterations) and the 10,000 samples drawn from the posterior distribution are somewhat lower than would normally be recommended to achieve convergence. No evidence of convergence has been provided by the company. Please provide evidence of convergence in each of the NMA analyses.

Convergence was confirmed by evaluation of the three chains and visual inspection of Brooks-Gelman-Rubin (BGR) plots. An example of the history, density and BGR trace plots for HiSCR50 in the predominantly biologic-naïve population are presented in Figure 7. The history plots show good overlap between the chains, there are no unexplainable spikes or abnormalities in the posterior density and the red line on the BGR plots approach 1.0 on the right-hand side, therefore showing adequate convergence.

Figure 7 Trace plots, density plots, and Brooks-Rubin for HiSCR50 in the predominantly biologic-naïve network (fixed-effect PBO-adjusted model)



Abbreviations: HiSCR, Hidradenitis Suppurativa Clinical Response; PBO, placebo.

A25. If available, please supply the results of all NMAs for HiSCR outcomes using the random-effects model without placebo adjustment.

Goodness of model fit statistics suggest that the random-effects (RE) models are not the best fit models for the HS evidence base, likely due to the data sparsity. Model fit statistics are presented in Table 29.

However, as requested, the outputs from the random-effects models are provided in Table 30 - Table 32; these results are also presented in section D.1.5.7 of the company submission appendix.

Table 28 Goodness of fit statistics for HiSCR response outcomes

Model	HiSCR50 FE PBO-adjusted	HiSCR50 RE	HiSCR75 FE PBO-adjusted	HiSCR75 RE	HiSCR90 FE PBO-adjusted	HiSCR90 RE
Datapoints	23	23	19	19	19	19
Total residual deviance	24.43	20.98	19.34	18.32	14.64	20.47
Posterior variance	16.13	16.71	12.98	15.08	12.67	14.63
DIC	152.93	154.21	124.12	126.09	106.36	116.70
DIC rank	2	3	1	4	1	4
Alternative DIC	40.56	37.69	32.32	33.40	27.31	35.10
Alternative DIC rank	4	2	2	4	1	4
Between study SD (95% CrI)	NA	0.13 (0.01, 0.47)	NA	0.18 (0.00, 0.69)	NA	0.19 (0.01, 0.89)
Beta (95% CrI)	-1.09 (-2.41, 0.31)	NA	-1.20 (-2.30, -0.00)	NA	-1.04 (-1.36, -0.95)	NA
Average residual deviance	1.06	0.91	1.02	0.96	0.77	1.08

CrI, credible interval; DIC, deviance information criterion; FE, fixed-effects; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; NA, not available; PBO, placebo; RE, random-effects; SD, standard deviation

Table 29 Key results for HiSCR50 analysis (mNRI HS-ABX; RE without PBO-adjustment)

	PBO	BKZ Q2W	BKZ Q4W	SEC Q2W	SEC Q4W	ADA QW
Trt vs PBO; OR (95% CrI)	Reference	**2.85 (1.87, 4.50)**	**2.68 (1.67, 4.43)**	**1.62 (1.07, 2.43)**	**1.63 (1.07, 2.48)**	**2.62 (1.90, 3.62)**
Trt vs PBO; RR (95% CrI)	Reference	**1.82 (1.48, 2.19)**	**1.77 (1.39, 2.17)**	**1.36 (1.05, 1.70)**	**1.37 (1.05, 1.71)**	**1.75 (1.49, 2.02)**
BKZ Q2W vs Trt; OR (95% CrI)	**2.85 (1.87, 4.50)**	Reference	1.06 (0.72, 1.60)	1.74 (0.98, 3.27)	1.73 (0.95, 3.26)	1.09 (0.66, 1.83)
BKZ Q2W vs Trt; RR (95% CrI)	**1.82 (1.48, 2.19)**	Reference	1.03 (0.87, 1.24)	1.33 (0.99, 1.84)	1.32 (0.98, 1.84)	1.04 (0.82, 1.30)
Probability BKZ Q2W better than treatment (Mean)	100.0%	NA	63.1%	97.1%	96.7%	63.9%
SUCRA (mean)	0.6%	84.2%	75.9%	32.1%	32.1%	75.1%
Absolute response (95% CrI)	30.5% (27.7%, 33.5%)	55.6% (44.5%, 66.8%)	54.0% (41.8%, 66.3%)	41.7% (31.5%, 52.2%)	41.7% (31.6%, 52.7%)	53.4% (44.7%, 62.0%)
Rank 1 probability (mean)	0.0%	43.1%	27.0%	0.5%	0.7%	28.8%

Statistically significant results are highlighted in **bold**

ABX, antibiotics; ADA, adalimumab; BKZ, bimekizumab; CrI, credible interval; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; NA, not available; OR, odds ratio; PBO, placebo; QW, every week; Q2/4W, every 2/4 weeks; RE, random-effects; RR, relative risk; SEC, secukinumab; SUCRA, surface under the cumulative ranking curve; Trt, treatment.

Table 30 Key results for HiSCR75 analysis (mNRI HS-ABX; RE without PBO-adjustment)

	PBO	BKZ Q2W	BKZ Q4W	SEC Q2W	SEC Q4W	ADA QW
Trt vs PBO; OR (95% CrI)	Reference	**3.72 (2.16, 6.61)**	**2.82 (1.50, 5.22)**	**1.87 (1.08, 3.23)**	**2.03 (1.19, 3.53)**	**2.66 (1.58, 4.50)**
Trt vs PBO; RR (95% CrI)	Reference	**2.64 (1.84, 3.61)**	**2.21 (1.40, 3.22)**	**1.65 (1.07, 2.42)**	**1.76 (1.16, 2.56)**	**2.13 (1.45, 2.96)**
BKZ Q2W Vs Trt; OR (95% CrI)	**3.72 (2.16, 6.61)**	Reference	1.31 (0.83, 2.23)	1.98 (0.92, 4.57)	1.82 (0.84, 4.10)	1.40 (0.71, 2.85)
BKZ Q2W Vs Trt; RR (95% CrI)	**2.64 (1.84, 3.61)**	Reference	1.19 (0.89, 1.70)	1.59 (0.94, 2.79)	1.49 (0.89, 2.57)	1.24 (0.80, 1.97)
Probability BKZ Q2W better than treatment (Mean)	100.0%	NA	90.5%	96.0%	94.0%	84.5%
SUCRA; Mean	0.6%	93.0%	65.2%	34.1%	42.6%	64.6%
Absolute response (95% CrI)	14.9% (12.7%, 17.5%)	39.6% (26.9%, 54.2%)	33.1% (20.5%, 48.7%)	24.8% (15.6%, 37.0%)	26.3% (16.9%, 39.0%)	31.8% (21.2%, 45.1%)
Rank 1 %; Mean	0.0%	74.7%	7.2%	1.6%	3.5%	13.0%

Statistically significant results are highlighted in **bold**

ABX, antibiotics; ADA, adalimumab; BKZ, bimekizumab; CrI, credible interval; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; OR, odds ratio; PBO, placebo; QW, every week; Q2/4W, every 2/4 weeks; RE, random-effects; RR, relative risk; SEC, secukinumab; SUCRA, surface under the cumulative ranking curve; Trt, treatment.

Table 31 Key results for HiSCR90 analysis (mNRI HS-ABX; RE without PBO-adjustment)

	PBO	BKZ Q2W	BKZ Q4W	SEC Q2W	SEC Q4W	ADA QW
Trt vs PBO; OR (95% CrI)	Reference	**4.10 (2.03, 9.46)**	**3.73 (1.68, 9.06)**	**2.08 (1.03, 4.31)**	**2.43 (1.25, 4.99)**	**2.34 (1.26, 4.64)**
Trt vs PBO; RR (95% CrI)	Reference	**3.34 (1.88, 5.88)**	**3.11 (1.60, 5.73)**	**1.93 (1.03, 3.49)**	**2.20 (1.22, 3.88)**	**2.13 (1.24, 3.69)**
BKZ Q2W Vs Trt; OR (95% CrI)	**4.10 (2.03, 9.46)**	Reference	1.10 (0.63, 2.13)	1.93 (0.73, 5.89)	1.67 (0.63, 5.04)	1.74 (0.74, 4.45)
BKZ Q2W Vs Trt; RR (95% CrI)	**3.34 (1.88, 5.88)**	Reference	1.07 (0.72, 1.79)	1.70 (0.77, 4.00)	1.50 (0.69, 3.57)	1.56 (0.78, 3.18)
Probability BKZ Q2W better than treatment; Mean	100.0%	NA	65.1%	90.9%	85.2%	90.2%
SUCRA; Mean	0.8%	86.3%	76.8%	37.8%	51.9%	46.5%
Absolute response (95% CrI)	7.2% (5.6%, 9.1%)	24.1% (13.0%, 43.1%)	22.4% (11.1%, 41.9%)	13.9% (7.1%, 26.1%)	15.8% (8.3%, 28.9%)	15.4% (8.5%, 27.4%)
Rank 1 %; Mean	0.0%	52.6%	29.1%	3.4%	9.4%	5.5%

Statistically significant results are highlighted in **bold**

ABX, antibiotics; ADA, adalimumab; BKZ, bimekizumab; CrI, credible interval; HiSCR, Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; mNRI, modified non-responder imputation; NA, not available; OR, odds ratio; PBO, placebo; QW, every week; Q2/4W, every 2/4 weeks; RE, random-effects; RR, relative risk; SEC, secukinumab; SUCRA, surface under the cumulative ranking curve; Trt, treatment.

A26. If feasible, please supply NMAs for HiSCR outcomes using the “All ABX” approach to excluding patients with antibiotic use for the BE HEARD trials.

Differences in calculation of the outcome measures based on alternative definitions of antibiotic intercurrent events and missing data handling strategies necessitated recalculation of the endpoints for HS0001 and BE HEARD I and II using the patient-level data to match as closely as possible the imputation and intercurrent event methods reported in the comparator studies, especially secukinumab. This increased the comparability of the outcome data between the studies. Table 33 illustrates the bias that using antibiotic intercurrent event (ALL-ABX) versus antibiotic as rescue medication for HS (HS-ABX) intercurrent events, would create in the absence of similar data for comparators. Using ALL-ABX would increase the number of patients set to non-responders regardless of response status by up to 15% at the week 16 primary endpoint timepoint. All-ABX estimand data were only available for the bimekizumab BE HEARD studies and were not available for comparator studies. Therefore, an NMA using All-ABX data is not appropriate.

Table 32 Summary of Intercurrent Events During the Initial Treatment Period (RS)

	BE HEARD I			BE HEARD II		
	PBO N=72 n (%)	BKZ 320mg Q4W N=144 n (%)	BKZ 320mg Q2W N=289 n (%)	PBO N=74 n (%)	BKZ 320mg Q4W N=144 n (%)	BKZ 320mg Q2W N=291 n (%)
Intercurrent event summary (All-ABX)						
All intercurrent events	16 (22.2)	28 (19.4)	52 (18.0)	7 (9.5)	19 (13.2)	53 (18.2)
All antibiotic rescue medication intercurrent event (ALL-ABX)	15 (20.8)	22 (15.3)	47 (16.3)	6 (8.1)	18 (12.5)	45 (15.5)
Discontinued due to adverse event	1 (1.4)	6 (4.2)	5 (1.7)	1 (1.4)	1 (0.7)	8 (2.7)
Discontinued due to lack of efficacy	0	0	0	0	0	0
Intercurrent event summary (HS-ABX)						
All intercurrent events	5 (6.9)	8 (5.6)	19 (6.6)	5 (6.8)	8 (5.6)	22 (7.6)
Physician-identified antibiotic rescue	4 (5.6)	2 (1.4)	12 (4.2)	4 (5.4)	7 (4.9)	14 (4.8)

medication (HS-ABX)						
Discontinued due to adverse event	1 (1.4)	6 (4.2)	7 (2.4)	1 (1.4)	1 (0.7)	8 (2.7)
Discontinued due to lack of efficacy	0	0	0	0	0	0

A27. Please clarify how the two BE HEARD trials and the SUNRISE/SUNSHINE trials were combined in the NMAs. Were the raw data pooled for the trials, or were they treated as separate trials within the NMA?

Where data allowed, the NMAs used raw data from the individual trials as inputs. In several analyses, data were not available separately by trial for the comparator. A summary of NMA trial pooling is provided in Appendix D.1.5.2 of the company submission and is also summarised below:

- All patients:
  - Bimekizumab BE HEARD I/II: Achieving improvement in International Score Hidradenitis Suppurativa Severity ≥55% (IHS4-55)
  - Secukinumab trials SUNRISE and SUNSHINE: change from baseline (CFB) in IHS4; IHS4-55; CFB in draining tunnel (DT) count; worst skin pain (NRS30)
- Prior biologic-experienced subgroup:
  - Bimekizumab BE HEARD I/II: HiSCR50
  - Secukinumab trials SUNRISE and SUNSHINE pooled data, prior biologic-experienced subgroup: HiSCR50; % CFB in AN.

A28. Please clarify how or if the Q2W/Q4W arm of the BE HEARD trials was used in the NMAs, given that is the approved dosing schedule. If available, please provide NMA results for HiSCR outcomes using the approved Q2W/Q4W bimekizumab dosing schedule as the reference arm.

Given that the randomized Q2W/Q4W and Q2W/Q2W dosing regimens are identical (Q2W) to Week 16, 16-week analyses from BE HEARD I/II are based on all subjects receiving Q2W dosing to Week 16 (i.e., the Q2W/Q4W and Q2W/Q2W arms combined).

MAICs

A29. The matching process for the MAIC analyses appears to have produced a perfect matching (to 2 d.p.) for all matched characteristics (see Tables 112 and 113 in Section D.1.6.2). This seems highly implausible given matching is performed over 24 parameters. Could the company please confirm if these tables are correct, supply corrections if not, or provide an explanation as to how such a perfect matching was achieved.

The MAIC analysis was performed according to the methods described in Appendix D of the NICE DSU Technical Support Document 18 [12]. The baseline characteristics are outcome-agnostic, such that they are only dependent on the baseline characteristics of the competitor/comparator treatment(s) and trial(s). Thus, the number of parameters does not factor into the weighting. For comparisons against secukinumab we matched on 12 baseline characteristics, with any bimekizumab subjects with missing baseline characteristics omitted. This resulted in 291 of 292 subjects being weighted. Once, weighted the effective sample size and summary statistics were obtained. The BE HEARD and SUNRISE/SUNSHINE trials were similar enough in baseline characteristics for no issues to arise in matching. However, the ESS does drop accordingly, and reflects the differences in baseline characteristics between the trials. The weights assigned to the BE HEARD patients also illustrate that the differences between the trials are appropriately accounted for. The programs used to derive matching, weighting, and outcomes for the MAIC are provided in a confidential supplement to this document [13].

A30. Please clarify how the two BE HEARD trials and the SUNRISE/SUNSHINE trials were “pooled” in the MAICs. Were the raw data pooled for the trials, or were they pooled using meta-analysis or other statistical methods?

For BE HEARD I and II we had individual patient data available, which were pooled programmatically (not by meta-analysis or any statistical methodology). It is effectively “stacking” the data into one ADAM dataset. For the competitor trials pooling was done using weighting. We utilized the treatment n’s for weighting of obtained weighted mean/proportions and pooled standard deviations.

Adverse Events

A31. Please clarify the patient numbers in Table 50; did 657 patients enter the BE HEARD EXT study, of which 604 had at least one dose of BKZ 320 mg Q2W and 507 patients had at least one dose of BKZ 320 mg Q4W? Is there a reason why the proportion of patients in the 'Total' column who experienced each of the adverse events is [redacted] than the previous (individual dose) columns?

Yes, 657 patients entered the BE HEARD EXT study and 604 were exposed to BKZ 320 mg Q2W and 507 patients were exposed to BKZ 320 mg Q4W. Any adverse event that had onset while the patient was receiving BKZ 320 mg Q2W or BKZ 320 mg Q4W are counted in the respective column. If the patient had any adverse event while receiving BKZ they are counted in the BKZ total column. Because there are patients who were exposed to both doses there are a number of patients who had an adverse event onset while on one dose but not the other. These patients would therefore be included in either the BKZ 320 mg Q2W column or the BKZ 320 mg Q4W column. They would all be included in the BKZ column, leading to a higher percentage overall of patients experiencing an adverse event overall than when counting onset on a particular dose.

A32. "Hidradenitis" is listed as an adverse event (Table 51, document B). Please clarify, as this adverse event seems to be synonymous with the treated disorder itself.

The most frequently reported treatment-emergent adverse event in the bimekizumab total group (S1 pool) was hidradenitis This adverse event is a combination of different reported terms, with the most frequently reported terms related to HS abscesses, pain due to HS, and worsening of HS. As HS is a cyclic disease and patients are expected to have flares of lesions and symptoms it is reasonable and expected to monitor these events.

Section B: Clarification on cost-effectiveness data

Treatment discontinuation and stopping rules

B1. Clinical advice to the EAG (and the TA925 FDG) suggests clinicians would wait at least 12 weeks before withdrawing treatment due to secondary non-response.

Section B.3.2.3.2 describes a stopping rule based on three consecutive cycles of non-response for secukinumab during maintenance treatment, but it is not clear whether this stopping rule is intended to also apply to bimekizumab. Please clarify how you intend stopping rules to be applied during the maintenance phase on bimekizumab.

UCB confirms that the modelling of primary and secondary non-responders in bimekizumab is accurate and in line with the bimekizumab clinical trial data and the implementation of stopping rules in economic models. During the maintenance phase on bimekizumab, secondary non-responders should discontinue treatment immediately.

B2. Priority: It is unclear whether treatment discontinuation on bimekizumab and secukinumab is modelled as intended. The model should consider three different types of discontinuation – primary non-response, secondary non-response, and discontinuation for other reasons (beyond Week 16).

a. **All discontinuing patients currently pass through the same set of tunnel states and are immediately switched to BSC costs and transition probabilities. This is appropriate for primary non-response and other post-Week 16 discontinuation, but not for secondary non-responders. These first groups should move immediately to BSC - please correct this.**

b. **Secondary non-responders are currently modelled to discontinue treatment immediately at the point of non-response. These patients should pass through a separate series of tunnel states in which treatment is continued and bimekizumab/secukinumab transition probabilities are applied. If response is regained, they should remain on treatment in their new response category. Please check and correct.**

The model does not differentiate by primary or secondary non-response. Both primary and secondary non-responders immediately switch to BSC. The description of a tunnel state for secondary non-response in the company submission was in error.

The inclusion of a tunnel state for secukinumab non-responders in TA935 was consistent with secukinumab's licence, which includes up-titration. The company in TA935 included a 12-week period to assess the effectiveness of up-titration from the Q4W to Q2W secukinumab dose. Because secukinumab has a non-confidential flat price discount to allow Q2W dosing to be supplied at the same cost as Q4W dosing, a tunnel state is not needed in this model.

The primary effect of such a tunnel state would be to reduce discontinuation from secukinumab to BSC. In order to model this, UCB has conducted a scenario where the stopping rule for secukinumab is relaxed in line with transition probabilities from HiSCR<25 to any other state up to week 48. The results of the analysis (Table 34) showed minimal effect on the ICER. This scenario includes modifications made in response to B3.

Table 33 Scenario relaxing stopping rule for secukinumab to week 48

Scenario	Treatment	Total		Incremental		ICER (£/QALY) (BKZ vs comparator)
		Costs	QALYs	Costs	QALYs	
Base Case	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£ 12,444
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£ 3,605
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	
SEC stopping rule in HiSCR<25 state = [redacted] to week 48	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£ 12,444
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£ 3,820
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	

B3. Priority: Treatment discontinuation rates in the executable model appear much higher than implied by the rates discussed in the submission, with only 10% of patients remaining on treatment at Year 2.

a. The CS states that discontinuation risk was set at 0.47% per 4-week cycle beyond Week 48, in line with previous appraisals, but the model appears to apply a rate of 2.08% per cycle after Week 48. Please check and correct.

As noted by the EAG, the model produces higher discontinuation rates than intended. UCB has corrected this discrepancy. Moreover, UCB agree with the EAG contention that the stopping rule currently double counts patients who discontinue for lack of efficacy. In order to remedy this, UCB have calculated the proportion of patients who discontinue due to adverse events on the licenced bimekizumab dose regimen and used this to model discontinuation from week 16 onwards for patients who have response of HiSCR25 or higher. Please see the calculation Table 35.

Table 34 Discontinuation from bimekizumab between weeks 16 and 48 in the BE HEARD studies

Trial data	Discontinue due to AE	Number at risk	Week 16 to 48 rate	4 week probability
BKZ Q2W/Q4W	[redacted]	181	[redacted]	[redacted]

The [redacted] probability of discontinuation due to adverse events is closely aligned with the 0.47% probability of discontinuation from Corbett et al. 2016 that was used in TA935 [7, 14].

Updating the model changes the base case ICER versus secukinumab from £1,832/QALY to £3605/QALY and the ICER versus BSC from £12,299/QALY to £12,444/QALY. Secukinumab remains extendedly dominated by bimekizumab in the fully incremental analysis. The updates to the model change the ICERs for all scenarios, see table below.

Table 35: Base case and scenario analyses with revised discontinuation risk past week 16

Scenario	Treatment	Total		Incremental		ICER (£/QALY)	
		Costs	QALYs	Costs	QALYs	CQ results	Δ in ICER from CS: CQs results – CS results
Basecase	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,444.01	£145.42
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,605.07	£1,772.75
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
1	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,549.77	£115.62
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,670.74	£1,741.33
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
2	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£21,703.62	£109.20

	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£10,033.87	£2,257.84
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
3	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£48,050.78	-£651.89
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£23,459.72	£3,018.32
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
4	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,444.01	£145.42
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,420.72	£1,729.43
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
5	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£86,760.11	-£4,405.06
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£47,621.31	£694.79
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
6	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£81,613.33	-£4,335.92
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£43,606.61	£715.53
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
7	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£88,490.86	-£4,699.89
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£48,158.89	£553.11
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
8	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,424.46	£143.21
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,584.72	£1,767.62
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
9	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,971.66	£163.49
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£2,501.56	£2,147.37
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
10	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,175.52	£204.41
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	BKZ dominates	No difference
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
11	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,838.54	£322.83
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£5,791.50	£2,193.87
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
12	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,225.68	£447.30
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£2,342.44	£1,203.00
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
13	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,619.08	£152.76
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,832.38	£1,784.83
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		

Mortality

B4. Priority: It is the EAG's understanding that mortality in the HS population often relates to longstanding comorbidities linked to obesity, such as diabetes

and heart disease, and stroke, which are not typically reversed during response to available biologics.

a. Please provide further justification for the base case assumption that only non-responders experience disease-related mortality.

b. Please provide a scenario where disease-related mortality is applied to all patients regardless of response status.

c. Please justify the use of the crude HR (1.86) over the adjusted HR (1.48) with reference to the methods of adjustment.

UCB has not identified any evidence to inform the distribution of mortality risk based on HiSCR response levels. The company submission (CS) model assumed that patients in the non-response state would have an increased mortality risk. The rationale for this followed the assumption that the severity of HS is a causal factor in comorbidities that contribute to increased mortality. Therefore, individuals with worsening response levels to treatment would be expected to face higher mortality risk, while patients with mostly resolved HS would bear lower mortality. The current CS base-case assumption may underestimate the mortality risk for those in the most severe health states.

The rationale for this followed the assumption that the severity of HS is a causal factor in comorbidities that contribute to increased mortality. Therefore, individuals with worsening response levels to treatment would be expected to face higher mortality risk, while patients with mostly resolved HS would bear lower mortality.

The current CS base-case assumption may underestimate the mortality risk for those in the most severe health states. The impact of all patients experiencing disease-related mortality was tested in a scenario analysis. This scenario incorporates assumptions described in clarification question B3. When bimekizumab is compared with best supportive care the ICER changes from £12,444 per QALY in the CS model to £14,127 when disease related mortality was applied to all patients regardless of response. When compared with secukinumab, The ICER decreased from £3,605 to £1,272.

Table 36 Results of scenario analysis investigating the impact of all patients experiencing disease related mortality.

Scenario	Treatment	Total		Incremental		ICER (£/QALY) (BKZ vs comparator)
		Costs	QALYs	Costs	QALYs	
Base Case	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,605
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,444
All patients experience disease-related mortality.	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£1,272
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,127

Health-related quality of life

B5. Priority: Please present (or highlight) data demonstrating the significance of the modelled improvement in utility in the maintenance period vs the initial treatment period.

a) Please present a reanalysis of EQ-5D-3L data from the BE HEARD studies which does not separate data by treatment phase.

Please find below tables reporting the utility values used in the CS model base case (treatment specific, Table 38) and utility values from the BE HEARD studies that are neither treatment nor phase specific (Table 39).

The impact of using the pooled utilities (Table 39) in the cost-effectiveness analysis was tested in a further scenario analysis, the results of which are displayed in Table 40. The impact to the ICER was minimal compared to the revised base case model results for both comparisons (secukinumab or BSC).

Table 37 Base case utility values (phase specific)

Response	Active treatments		BSC	
	Initial	Maintenance	Initial	Maintenance
Non-Response (HiSCR<25)	[redacted]	[redacted]	[redacted]	[redacted]
Partial Response (HiCSR25)	[redacted]	[redacted]	[redacted]	[redacted]
Response (HiSCR50)	[redacted]	[redacted]	[redacted]	[redacted]
High Response (HiSCR75)	[redacted]	[redacted]	[redacted]	[redacted]

Very High Response (HiSCR90)	[redacted]	[redacted]	[redacted]	[redacted]

Table 38 Pooled utility values (not phase-specific)

Response	All treatments
	Initial or maintenance
Non Response (HiSCR<25)	[redacted]
Partial Response (HiCSR25)	[redacted]
Response (HiSCR50)	[redacted]
High Response (HiSCR75)	[redacted]
Very High Response (HiSCR90)	[redacted]

Table 39 Scenario analysis investigating the impact of using non phase specific pooled utilities

Scenario	Treatment	Total		Incremental		ICER (£/QALY) (BKZ vs comparator
		Costs	QALYs	Costs	QALYs	
Base Case	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,605
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,444
Pooled utilities (not phase-specific)	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£4,166
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,629

B6. Priority: Please present a reanalysis of EQ-5D-3L data from the BE HEARD studies which estimates utility based on level of response, regardless of which treatment received.

Please find below the utility values from the phase specific pooled analysis (Table 41) and the resultant impact on the cost effectiveness (Table 42) as tested in a further scenario analysis. The difference ICER across both comparisons was minimal (secukinumab or BSC).

Table 40 Pooled utilities (phase specific)

Response	All treatments	
	Initial	Maintenance
Non-Response (HiSCR<25)	[redacted]	[redacted]

Partial Response (HiCSR25)	[redacted]	[redacted]
Response (HiSCR50)	[redacted]	[redacted]
High Response (HiSCR75)	[redacted]	[redacted]
Very High Response (HiSCR90)	[redacted]	[redacted]

Table 41 Results of scenario analysis investigating the impact of using phase specific pooled utilities

Scenario	Treatment	Total		Incremental		ICER (£/QALY) (BKZ vs comparator
		Costs	QALYs	Costs	QALYs	
Base Case	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,444
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,605
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	
Pooled utilities (not phase-specific)	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£16,738
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£4,629
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	

B7. Please comment on the plausibility of the decrease in HRQoL modelled for placebo patients who achieve a high response (0.746) vs a response (0.767).

a) How many patients contributed data to each health state utility, by treatment arm?

b) Please comment on the appropriateness of using utilities based only on response level for all response levels above non-response.

The decrease in HRQoL for patients with high response ([redacted]) from the level for patients with response ([redacted]) is attributable to low numbers of placebo observations for these response states. Across all placebo subjects and initial period visits, a total of [redacted] response and [redacted] high response observations were included in the repeated measures ANCOVA models used to obtain utility estimates.

UCB conducted sensitivity analysis to explore the impact of pooled utility values over high-response (HiSCR75), which is the point the HRQL value drops below the response level. In the scenario presented below, the utility values in health states Non-response, Partial response and Response remained the same as in the base case (treatment-related). The utility values for High response and Very-high

response in the model were replaced with pooled values from the BE HEARD study (Table 43). A logical increase in the HRQoL is maintained across all health states from Non response to Very high response.

Table 44 presents the results of the scenario. There is very little change in the total QALYs for each comparator and the resulting ICER.

Table 42 Revision to replace treatment-related with pooled utility values for patients in health states high-response and above (>HiSCR75)

		Active treatment (BKZ or SEC)	BSC
Initial treatment phase	Non Response (HiSCR<25)	[redacted]	[redacted]
	Partial Response (HiCSR25)	[redacted]	[redacted]
	Response (HiSCR50)	[redacted]	[redacted]
	High Response (HiSCR75)	[redacted]	[redacted]
	Very High Response (HiSCR90)	[redacted]	[redacted]
Maintenance	Non Response (HiSCR<25)	[redacted]	[redacted]
	Partial Response (HiCSR25)	[redacted]	[redacted]
	Response (HiSCR50)	[redacted]	[redacted]
	High Response (HiSCR75)	[redacted]	[redacted]
	Very High Response (HiSCR90)	[redacted]	[redacted]

Table 43 Results of scenario with pooled HRQoL for patients HiSCR>75

	Treatment	Total		Incremental		ICER (£/QALY)
		Costs	QALYs	Costs	QALYs	
Basecase	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,444.01
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,605.07
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	
Use the same utility values for active treatment and BSC for HiSCR>75	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£11,753.94
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,403.55
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	

Resource use

B8. Priority: Please provide more recent and UK relevant data on the continued use of adalimumab following loss of response, i.e. a BSC comparator including 20.8% adalimumab. Clinical advice to the EAG suggests this would

now be unlikely to occur in practice given the availability of secukinumab on the NHS.

Please see the company response to question A4 for an explanation of the rationale of including some adalimumab use in BSC. UCB's current assumptions are in line with clinical feedback that some patients remain on adalimumab even after a loss of response. Some patients may continue on treatment with limited effective treatments to switch to with clinicians best placed to decide what is most clinically appropriate for these patients.

UCB would expect that patients who lose response when no more effective treatments are available could remain on current therapy with declining response, undertake re-treatment of a previously effective drug or receive BSC only. The clinical experts present for the NICE TA935 committee meetings noted that patients receiving BSC only would be more likely to have their condition worsen. The EAG clinical advisor supported some level of durable response on BSC. As such the company base-case includes use of adalimumab in BSC as a plausible option used within clinical practice.

Sensitivity analysis investigating the impact of including or excluding adalimumab usage in BSC was conducted. The impact on the reported ICER was minimal. Please see scenario 3 in the CS.

B9. Please justify the modelled assumption that patients receive adalimumab following failure on bimekizumab or secukinumab. Following failure on two lines of biologics it seems implausible that clinicians would reinitiate adalimumab.

Please see A4 and B8 for further explanation. Because biologics act on the underlying disease mechanisms of HS, even patients who have lost HiSCR25 response can be expected to receive some benefit in terms of reduction of AN or improvement in quality of life by remaining on a therapy that does not give them a HiSCR25 response, or re-initiating a previously tolerated and effective therapy where response was lost. It is important to remember that HiSCR response is lost if a patient has an increase in abscess count or draining fistula count relative to baseline, regardless of their reduction in AN count. Patients can have a large reduction in AN and be HiSCR25 non-responders.

B10. The model does not appear to include calculate treatment costs on TraceINT and TraceSEC for secondary non-responders. Non-responders should incur treatment costs during these 12 weeks, as should those patients who regain a response and remain on treatment. Please correct this in addition to the issue highlighted in Question B2.

The model does not currently include a tunnel state to allow secondary non-responders to remain on treatment. On the active therapy model sheets, columns BX through DH give the appearance of being tunnel states, but do not function as such. These columns are associated with patients who have stopped therapy. The cost column for active therapy costs (IS) does not include these columns, while column IW calculates BSC costs for these columns.

In the company response to clarification question B2 (part a) UCB has provided a scenario which reduces the proportion of patients who stop treatment for secukinumab. This was designed to simulate the effect of a tunnel state in the absence of implementation of a tunnel state within the model.

B11. Approximately 78% of total first-line treatment costs on bimekizumab are incurred in the first year, with acquisition costs dropping from ~£15,500 in Year 1 to £2,800 in Year 2. If this is not resolved in changes to the model requested previously, please comment on the plausibility of this trend with reference to total treatment costs in previous STAs (e.g. Yr1 £17,357 -> Yr2 £10,963 in TA392

In line with B3, the model has been updated. After the updates described in B3, cells IS44 through IS56 were added to cells IU44 through IU56 on the TraceINT (bimekizumab model arm) sheet in the model to calculate first year costs. This resulted in a total of £17,083 in drug costs over the first year. To calculate the costs in the second year, cells IS57 through IS69 were added to cells IU57 through IU69. This resulted in total costs for the second year of £6,423 for the bimekizumab arm.

B12. Priority: Estimates of long-term surgery and hospital resource use appear to have been obtained from a survey of n=40 clinical experts conducted by AbbVie for the appraisal of adalimumab (TA392).

a) **Please clarify whether you have attempted to validate the resource use values with your clinical advisors. If so, please describe any methods/findings.**

b) **Please clarify whether you attempted to source long-term resource use data from the published literature or real-world data. If so, please provide further details on the methods and results of identified studies. If not, please consider conducting a literature review, presenting alternative estimates in scenario analyses.**

c) **The submission states that these values have been adjusted to severity to reflect the characteristics of BE HEARD I and II. Please clarify how these values were weighted.**

Clinical validation was not sought, instead the resource use estimates used in the submitted model were aligned with the resource use estimates re-weighted by the proportion of patients with moderate or severe disease from the BE HEARD I [15] and BE HEARD II [16] trials that informed the decision-making ICERs used by the Committee in TA935 [7].

The company conducted economic SLRs in 2023 in an attempt to identify estimates of resource use for patients with moderate-to-severe HS. NICE TA392 [17] and Willems et al., (2020) [18] were identified as the only two publications relevant to the UK population. For full details of the literature review please see Appendix G of the Company Submission.

Mean annual HCRU is based on the original AbbVie survey data by health state for moderate (see Table 43 below) and severe (see Table 44 below) patients but adjusted to the severity in BE HEARD trials i.e. 55.7% of patients with moderate stage at baseline, and the remaining 44.3% in severe stage. A weighted average of the two HCRU tables was used to create a single HCRU table by health state (for each HCRU item: 55.7% x value in Table 43 and 44.3% x value in Table 44).

Table 44 Resource use rates by health state for patients with moderate HS

Resource	Annual resource use per health state			
	High response	Response	Partial response	Non-response
Hospitalisations for HS surgery	0.14	0.17	0.29	0.82
Outpatient visits due to HS surgery	0.20	0.33	0.46	0.83
Visits to wound care due to HS surgery	0.07	0.20	0.26	0.38
Hospitalisations, non-surgery related	0.09	0.14	0.29	0.50
Routine outpatient visits	2.97	3.54	4.13	4.63
Visits to wound care not due to HS surgery	1.07	0.68	0.74	0.47
A&E visits	0.15	0.25	0.35	0.59

Table 45 Resource use rates by heath state for patients with severe HS

Resource	Annual resource use per health state			
	High response	Response	Partial response	Non-response
Hospitalisations for HS surgery	0.11	0.26	0.75	0.78
Outpatient visits due to HS surgery	0.23	0.37	0.84	1.03
Visits to wound care due to HS surgery	0.15	0.15	0.51	1.23
Hospitalisations, non-surgery related	0.12	0.30	0.38	0.42
Routine outpatient visits	3.22	3.48	4.69	4.73
Visits to wound care not due to HS surgery	0.35	0.31	0.56	0.43
A&E visits	0.08	0.16	0.57	0.56

B13. Table 67 (Page 146) of the company submission describes unit costs for each item of resource use sourced from NHS reference costs.

a) Please provide details of any clinical advice sought regarding the setting of care (e.g., day case, elective) for each HRG code included and which setting/service codes were selected for each reference cost.

b) Please clarify how reference costs were weighted where multiple HRG codes were selected and describe any underlying assumptions (e.g., regarding proportion of surgeries that were inpatient etc.).

c) Please discuss what type of medical events make up patients requiring hospitalisation for 'non-surgery related' reasons.

Clinical advice was not sought, instead the HRG codes used in the submitted model were aligned with a previous submission (TA935 [7]).

Please find the calculations for the weighted averages derived from the NHS reference costs below. The weights were computed by diving the number of events per HRG code by the sum of all the events included in the specified cost group category.

Table 46 Weighted average calculation for cost of hospitalisation for HS surgery

Codes	Value (£)	Number of events	Weights
JC40Z (elective)	17209.58	232	0.022825659
JC41Z (elective)	8724.08	1353	0.133116883
JC42C (elective)	2511.31	4323	0.425324675
JC43C (elective)	859.27	4256	0.418732782
Total	2982.09	10164	

Table 47 Weighted average calculation for cost of non-surgery related hospitalisation

Codes	Value (£)	Number of events	Weights
JD07D	3808.07	9147	0.136193085
JD07K	1314.72	58015	0.863806915
Total	1654.29	67162	

Table 48 Weighted average calculation for cost of an A&E visit

Codes	Value (£)	Number of events	Weights

VB01Z	819.69	30648	0.001963222
VB02Z	725.67	400254	0.025639115
VB03Z	425.92	1281160	0.08206741
VB04Z	545.56	1107995	0.07097496
VB05Z	392.25	311112	0.019928936
VB06Z	296.79	437204	0.028006026
VB07Z	302.29	2269739	0.145392926
VB08Z	236.69	4974335	0.318641536
VB09Z	158.47	4798622	0.307385868
Total	278.10	15611069	

Table 49 Weighted average calculation for a mild-moderate upper respiratory tract infection

Outpatient codes (average)	Value (£)	Number of events	Weights
340	185.0740189	1752643	0.83831843
341	145.4160644	338022	0.16168157
Total	178.66	2090665	

Table 50 Weighted average calculation for heart failure

Codes	Value (£)	Number of events	Weights
EB03A	3633.809002	56126	0.28869617
EB03B	2691.000967	53118	0.27322388
EB03C	2012.131655	43375	0.22310866
EB03D	1525.041772	34437	0.17713413
EB03E	1030.443479	7356	0.03783717
Total	2542.36	194412	

Non-surgical hospitalisations for patients typically include a range of medical events. Based on previous submissions (TA392 [17]) and supported by Desai et al. 2017, these events often involve both non-elective and elective inpatient admissions [19]. Common conditions leading to such hospitalisations include cellulitis, psychiatric support, and the management of comorbidities and complications like bacterial infections. Additionally, Kimball et al. 2016, found that prolonged antibiotic treatment courses (over 90 days) significantly increased healthcare resource utilisation (HCRU) costs [20]. Inpatient stays, often due to antibiotic treatment failure, are a notable factor contributing to these higher costs.

Treatment effectiveness

B14. Priority: Please provide a full description of the methods used to estimate model transition probabilities using GLM for the bimekizumab treatment arm.

Transition probability matrices were derived for BKZ Q2W/Q4W using data from

- Week 0-16: all subjects initially randomized to BKZ Q2W (i.e., BKZ Q2W/Q2W and BKZ Q2W/Q4W combined)
- Week 16-48: all subjects randomized to BKZ Q2W/Q4W who met the relevant response criteria (per the model's stopping rule), at Week 16 (based on observed data)

Matrices were derived in accordance with the mNRI (HS-ABX) approach to handling missing data and intercurrent events. One hundred imputations of the data were considered using the mNRI (HS-ABX) approach. Within each imputation:

- Each subject was assumed to start in the non-response state (<HiSCR25) at Week 0
- For subsequent visits, each subject was assigned to a HiSCR response state, at each visit, in accordance with the mNRI (HS-ABX) approach.
- These response states were used to record all 4-weekly transitions from the relevant period (e.g., for Week 0-16, transitions were recorded for Week 0 → Week 4, Week 4 → Week 8, Week 8 → Week 12 and Week 12 → Week 16)
- Time invariant transition matrices were derived, so no further consideration was given to the pair of visits between which a transition was observed (other than the visits being 4 weeks apart)
- A generalised logit model was fitted to all four-weekly transitions from the relevant period (Weeks 0-16 or Weeks 16-48). The response variable was the receiving ('to') state of the transitions, with the starting ('from') state of the transitions included as an explanatory variable. No additional explanatory variables were included in the models.

The estimated probabilities of transitions, for each pair of 'from' and 'to' states (as estimated from the generalised logit models within each imputation) were averaged

across the 100 imputations to obtain the final estimates used in the transition probability matrices.

B15. Please provide a full description of the methods and data used to modify the bimekizumab transition matrix using risk ratios to generate transition probabilities for the comparator arms.

Please see B.3.3.2.1 within the CS. This section details the methodology utilised with the inclusion of mathematical formulae.

B16. Priority: Please present a scenario analysis in which transition probabilities are adjusted for the relative effectiveness of treatment in biologic experienced vs naïve patients according to the proportions of these groups in the trial vs the NHS population.

UCB did not identify any evidence on the NHS population distribution of biologic-experienced or biologic-naive patients. Therefore, an assessment of the overall generalisability of the model transition probabilities to the NHS population was not possible.

To inform the cost-effectiveness analysis, UCB replaced the transition probabilities of the base case (ITT population; CS Tables 56 and 58) with the probability matrices of patients in the BE HEARD clinical trial who were biologic-experienced and biologic-naive as an alternative scenario.

Table 50 and Table 51 present the transition matrices for the biologic-experienced; Table 52 and Table 53 present the transition matrices for the biologic-naive patients.

Table 51 Four-week transition probabilities for bimekizumab by HiSCR score; initial treatment period weeks 0-16; biologic-experienced subgroup

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HiSCR: hidradenitis supprativa clinical response.
Values in each cell represent the probability of transitioning from the initial HiSCR score level to the final HiSCR level within a 4-week cycle.

Table 52 Four-week transition probabilities for bimekizumab (Q2W/Q4W) by HiSCR score category in weeks 16-48; biologic-experienced subgroup

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HiSCR: hidradenitis suppurativa clinical response; Q2W, every 2 weeks; Q4W, every 4 weeks.

Values in each cell represent the probability of transitioning from the initial HiSCR score level to the final HiSCR level within a 4-week cycle.

Table 53 Four-week transition probabilities for bimekizumab by HiSCR score; initial treatment period weeks 0-16; biologic-naive subgroup

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HiSCR: hidradenitis supprativa clinical response.

Values in each cell represent the probability of transitioning from the initial HiSCR score level to the final HiSCR level within a 4-week cycle.

Table 54 Four-week transition probabilities for bimekizumab (Q2W/Q4W) by HiSCR score category in weeks 16-48; biologic-naive subgroup

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HiSCR: hidradenitis suppurativa clinical response; Q2W, every 2 weeks; Q4W, every 4 weeks.

Values in each cell represent the probability of transitioning from the initial HiSCR score level to the final HiSCR level within a 4-week cycle.

The results of each scenario are presented in the Table 54.

Table 55 CEM results for biologic-experienced and biologic-naïve patients

	Treatment	Total		Incremental		ICER (£/QALY) BKZ vs. comparator	ICER change from base case
		Costs	QALYs	Costs	QALYs		
Base case	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,444	
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,605	
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
Biologic experienced	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,531	£2,087
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£2,319	-£1,286
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		
Biologic naïve	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,061	-£383
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,939	£334
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]		

B17. Priority: Clinical advice received by the EAG indicates that patients on BSC (particularly those with moderate HS) can achieve long-term control of their condition. Patients may cycle through periods of relative control and flare, but permanent non-response may not appropriately represent the natural history of HS.

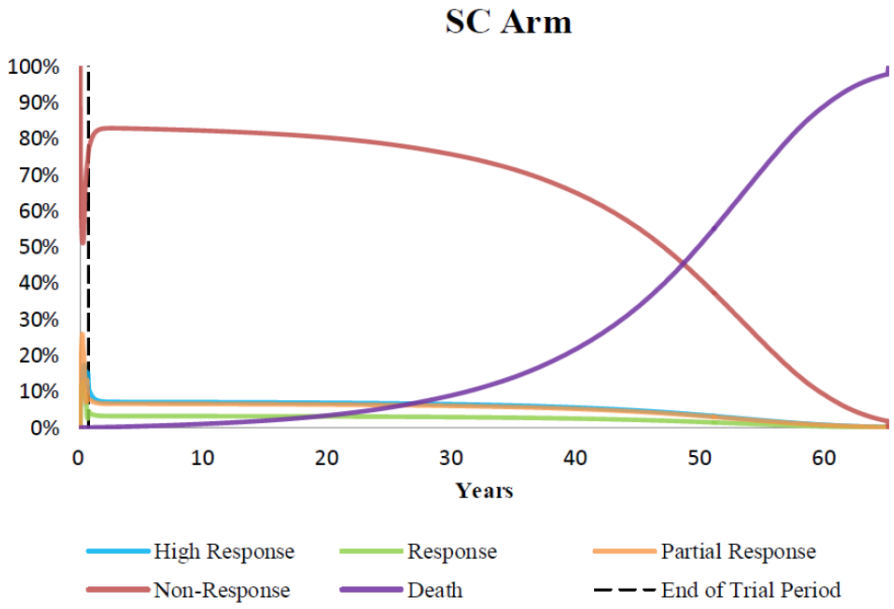
a) Please comment on the clinical validity of the assumption that patients on BSC rapidly and permanently lose any response achieved at Week 16 (partial or higher of 51.3%) by Week 48 (partial or higher of 4.8%). Please make reference to clinical input received by the company in support of this assumption.

In question B8, UCB note that the clinical experts in the TA935 committee meetings, supported the hypothesis that BSC would not maintain response in the long-term. This was also consistent with feedback UCB received in two UK advisory boards. The position of the EAG clinical adviser is consistent with the way that BSC was modelled in TA392 and in EAG scenarios conducted in TA935, and with how response to BSC is modelled in the UCB company submission after 48 weeks [7, 17]. In the UCB company submission three options were presented for modelling response for BSC between week 16 and week 48: a scenario where new response could not be gained that used data from BE HEARD transition probabilities (titled 'gradual deterioration'), a scenario aligned with TA935 that estimated loss of

response for BSC based on the 36 week PIONEER II placebo arm data [21], and a scenario that used the week 16 NMA against placebo to estimate BSC efficacy.

In addition, the model includes an option to do as the clinical advisor to the EAG and assumptions from TA392 and the EAG analyses in TA935 suggest, and allow long term response on BSC. This is accomplished by mirroring what is done in TA392, where the model trace shows that response is fixed at approximately 10.4% (the sum of response and high response in Figure 8) for BSC from approximately 48 weeks. UCB allowed long-term response on BSC to be fixed past 48 weeks, which produces a response on BSC of approximately 10.8% in the long-term.

Figure 8 Reproduction of Figure 25 from TA392 provided in company response to draft guidance in TA935



In order to allow more flexibility in how the two conflicting perspectives on long-term BSC efficacy should be modelled, UCB has produced an analysis that allows replicating PIONEER II up to week 36, while slowing long-term deterioration by applying a relative risk to the 9.6% probability per cycle of BSC patients becoming a non-responder from any state in the loss of response scenario described above. For the exploratory analysis below (Table 55), a relative risk of 0.1 is used after week 48 with the intention of having a greater number of patients exhibit durable response on BSC without fixing response in the long-term.

Table 56 BSC loss of response with slowing of response loss after week 48

Scenario	Treatment	Total		Incremental		ICER (£/QALY) (BKZ vs comparator)
		Costs	QALYs	Costs	QALYs	
Base Case	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,444
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£3,605
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	
BSC transition probabilities determined by NMA beyond week 16	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£50,546
	SEC	[redacted]	[redacted]	[redacted]	[redacted]	£25,334
	BKZ	[redacted]	[redacted]	[redacted]	[redacted]	

b) Please include a model scenario in which the RR for placebo vs bimekizumab is used to generate a BSC transition matrix for the maintenance phase.

This scenario is included in the submission. It corresponds to scenario 7 in Table 76 of the CS. This scenario produces high levels of placebo response, with [redacted] having a HiSCR50 response and [redacted] having a HiSCR25 response at week 48. Table 36 updates this scenario in line with question B3.

B18. Please provide a comparison of actual model health state residence at key time points on bimekizumab, secukinumab, and BSC, with the source data.

Please find below the following comparisons:

- HiSCR50 response in the placebo arm of PIONEER II compared to HiSCR response in the model at weeks 20-36 under three assumptions for week 16-48 efficacy for BSC (Table 56)
- HiSCR50 response (HS-ABX) as reported for the pooled bimekizumab Q2W induction arms of BE HEARD I and II at week 16 [22], and pooled OC bimekizumab data at week 48 in BE HEARD I and II [23], compared to HiSCR50 response among patients who have not discontinued 1st line therapy at week 16 and 48 in the model (Table 57)

- HiSCR50 response (HS-ABX) as reported for the pooled secukinumab Q4W arms of SUNSHINE and SUNRISE at week 16 [10], and pooled OC secukinumab data at week 52 in SUNSHINE and SUNRISE [10], compared to HiSCR50 response among patients who have not discontinued 1st line therapy at week 16 and 52 in the model (Table 58)

Table 57 Comparing HiSCR50 response reported for placebo in PIONEER II to economic model response status

Time	PIONEER II	Gradual deterioration (base case)	Loss of response only	NMA	Source
20	23.2%	[redacted]	[redacted]	[redacted]	PIONEER II data from Jemec et al. 2019 [21]
24	25.2%	[redacted]	[redacted]	[redacted]	
28	15.2%	[redacted]	[redacted]	[redacted]	
32	18.5%	[redacted]	[redacted]	[redacted]	
36	15.9%	[redacted]	[redacted]	[redacted]	

The gradual deterioration scenario matches well with descriptions given by UK dermatologists and advisory boards advising that response would decrease, but predicts less response than seen in PIONEER II. Loss of response only, matches well with PIONEER II data, because it is a linear model fit to PIONEER II data. The NMA scenario consistently overpredicts response observed in PIONEER II.

Table 58 Comparing HiSCR50 response reported by bimekizumab in the BE HEARD studies to economic model response status

Time	BE HEARD I & II pooled Q2W/[Q4W] HiSCR50	Model HiSCR50	Source
16	56.9%	[redacted]	Kimball et al. 2023 [AAD presentation] [22] HS-ABX (mNRI), all Q2W to 16 weeks
48	80.6%	[redacted]	Zouboulis et al. 2023 [EADV presentation] [23] OC, Model patients are only those who remain on initial treatment with half-cycle correction to mirror OC

Table 59 Comparing HiSCR50 response reported by secukinumab in the SUNSHINE and SUNRISE studies to economic model response status

Time	SUNSHINE & SUNRISE pooled (Q4W) HiSCR50	Model HiSCR50	Source
16	43.9%	[redacted]	Kimball et al. 2023 [10]
52	59.2%	[redacted]	Kimball et al. 2023 [10], Model patients are only those who remain on 1st line with half-cycle correction to mirror OC

For bimekizumab and secukinumab, the model provides consistent fit with trial data at week 16 and at approximately one year for the HiSCR50 outcome.

Probabilistic sensitivity analysis

B19. Where data allows, please use standard errors derived from the data source to sample probabilistic parameter values in the probabilistic sensitivity analysis.

UCB reviewed the model parameters sampled in PSA. The sampling of the unit costs that contributed to surgery hospitalisations, non-surgery hospitalisations, outpatient visits, and accident and emergency-related visits was updated.

A gamma distribution was used to sample outpatient visits and non-surgery hospitalisation costs, parameterised using the low and high values reported and assuming they reflected the 95% confidence interval limits.

Because of outliers within the surgery hospitalisations and A&E visits costs (for example, 3% of surgery-related hospitalisations cost over £17,000, whereas the weighted average was £3,000), a similar parameterisation of the gamma distribution would overestimate the precision estimate and generated spurious results. Instead, the lowest value of surgery hospitalisation was assumed to reflect the low limit of the 95% confidence interval and the difference between the weighted average mean and the lowest value was used to calculate the high limit of the 95% confidence interval.

Table 60 Weighted mean, assumed precision and probabilistic distribution for resource use variables

Resource use	Weighted mean (deterministic value)	Assumed SE (distribution)
Hospitalisations for HS surgery	£2,982.10	£761 (Gamma)
Hospitalisations non-surgery related	£1,654.30	£636 (Gamma)
A&E visits	£278.10	£71 (Gamma)
Outpatient visits due to HS surgery	£152.30	£6 (Gamma)
Visits to wound care due to HS surgery		
Routine outpatient visits		
Visits to wound care not due to HS surgery		

B20. Priority: Please clarify how relative risks applied to derive transition probabilities for each treatment and level of response were sampled in the PSA. These each appear to be independently sampled using the standard error. These parameters should be sampled jointly either using a variance-covariance matrix, or simply the NMA/MAIC CODA.

The sampling was modified to use CODA for the relative risks generated in the NMA by treatment and health state. Three chains per HiSCR with 60,000 simulations were available. Within each chain, a comparator treatment relative risk was simulated 10,000 times. Therefore, combined across three chains, a treatment has 30,000 simulations per HiSCR.

After implementation of the new sampling method for the relative risks, the results of the PSA (1,000 samples) are presented in Table 60, Table 61. The total cost and QALY values were similar to those generated in the CS.

The probabilistic analysis estimated the ICER for bimekizumab below the £20,000 per QALY threshold against both comparators. Secukinumab was extendedly dominated by bimekizumab.

Table 61 Fully incremental cost-utility probabilistic sensitivity analysis

	Total		Incremental (vs reference)		ICER vs reference (BSC): £/QALY
	Cost (£)	QALY	Cost (£)	QALY	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	–
SEC	[redacted]	[redacted]	[redacted]	[redacted]	£38,190.46 (extendedly dominated by BKZ)
BKZ	[redacted]	[redacted]	[redacted]	[redacted]	£19,420.18

BKZ, bimekizumab; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab.

Table 62 Pairwise comparisons probabilistic sensitivity analysis

	Total		Incremental (vs BKZ)		ICER vs BKZ: £/QALY
	Cost (£)	QALY	Cost (£)	QALY	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£19,420.18
SEC	[redacted]	[redacted]	[redacted]	[redacted]	£5,155.93
BKZ	[redacted]	[redacted]	[redacted]	[redacted]	–

BKZ, bimekizumab; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab.

The cost-effectiveness plane scatterplot and cost-effectiveness acceptability curve are in Figure 34 and Figure 35, respectively.

Figure 9 Cost-effectiveness plane scatterplot (confidential)

[redacted]

Q4W, once every four weeks; QALY, quality- adjusted life years; WTP, willingness-to-pay.

Figure 10 Cost-effectiveness acceptability curve (confidential)

[redacted]

Q2W, once every two weeks; Q4W, once every four weeks; QALY, quality-adjusted life years; WTP, willingness-to-pay.

Section C: Textual clarification and additional points

Search strategies

C1. A sentence from page 183, Section D.1.1, Appendix D appears to be incorrect:

"Search terms for specific treatments were used in the October 2023 search update but not in the original April 2023 search, because the latter was run as part of a broader SLR which included additional interventions (references for the additional interventions are not described further in this submission)."

The search strategies presented in Tables 77, 78, 79, 80, 81 and 82 appear to show the opposite – that terms for specific treatments were used in the April 2023 search but not in the October 2023 search. Please clarify.

This is a typing error in the submission document. The October 2023 search was run as part of a broader SLR and therefore did not contain search terms for specific treatments. Suggested edit below:

"Search terms for specific treatments were used in the April 2023 search but not in the October 2023 update search, because the update search was run as part of a broader SLR which included additional interventions (references for the additional interventions are not described further in this submission)."

C2. Please provide the following details for the conference abstract searches on page 183, Section D.1.1, Appendix D and the website searches on page 184, Section D.1.1, Appendix D:

a) The date that these searches were carried out

b) Search strategies used in each resource

Hand searches for the April 2023 SLR were conducted on April 21st 2023. Clinicaltrials.gov was searched using the disease term ('hidradenitis suppurativa') in the "condition/disease" field of the search engine. Conferences were searched with the disease term if a search engine was available on the conference website; the titles/abstracts of proceedings of the remaining conferences were hand searched.

The hand searching strategies for the October 2023 SLR update are provided below.

Table 63: Conference hand-searching strategy

Name of resource	Year of conference	Website	Date of search	Description of search	Keywords searched
American Academy of Dermatology (AAD)	2023	https://eposters.aad.org/	3rd November 2023	Search "AAD 2023" >> Click the "session handouts" link under the first search result >> click the "VMX and Annual Meeting posters" link under "Poster exhibits" Click "search" in the top right hand corner >> search abstracts using keywords	"adalimumab", "bimekizumab", "secukinumab"
European Academy of Dermatology and Venereology (EADV)	2023	https://eadv.org/scientific/abstract-books/	3rd November 2023	EADV Congress 2023>> Acne and related disorders, hidradenitis suppurativa >> CTRL F keywords	"adalimumab", "bimekizumab", "secukinumab"
European Hidradenitis Suppurativa Foundation (EHSF)	2023	https://onlinelibrary.wiley.com/doi/epdf/10.1111/exd.14898	2nd November 2023	Search "12th EHSF abstract book" >> click Pubmed link>> Open PDF via free full text link	"adalimumab", "bimekizumab", "secukinumab"
Professional Society for Health Economics and Outcomes Research (ISPOR) Europe	2023	https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-2023	3rd November 2023	Click "posters" in the "program" drop down >> search key word for each poster session.	"adalimumab", "bimekizumab", "secukinumab"

Table 64: HTA agency hand-searching strategy (includes expanded scope)

Name of resource	Website	Date of search	Description of search	Keywords searched
Institute for Clinical and Economic Review - USA	https://icer.org/	21st November 2023	Click “explore our research” >> select “assessments” >> enter keyword into search bar	“Hidradenitis suppurativa”
Scottish Medicines Consortium - Scotland	https://www.scottishmedicines.org.uk/	21st November 2023	Click “medicines advice” >> enter keyword into search bar under published medicines	“Hidradenitis suppurativa”
Canadian Agency for Drugs and Technologies in Health - Canada	https://www.cadth.ca/	21st November 2023	Enter keyword into the search bar in the top left corner.	“Hidradenitis suppurativa”
National Institute for Health and Care Excellence - England	https://www.nice.org.uk/	21st November 2023	Click “guidance” >> click “browse guidance >> enter keyword into search bar	“Hidradenitis suppurativa”
Institute for Quality and Efficiency in Health Care - Germany	https://www.iqwig.de/en/	21st November 2023	Click “projects and results” under “projects” >> Enter keyword into search term search box	“Hidradenitis suppurativa”
Gemeinsamer Bundesausschuss - Germany	https://www.g-ba.de/english/	22nd November 2023	Keyword in search bar >> Filter to benefit assessment procedures	“Hidradenitis”
Haute Autorité de Santé - France	https://www.has-sante.fr/	22nd November 2023	Search keyword in search bar	“hidradenitis”, “Hidradénite” (for English and French content)
Pharmaceutical Benefits Advisory Committee - Australia	https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd	22nd November 2023	Click Public Summary Documents by Product link >> CTRL F keywords	“Adalimumab”, “Bimekizumab”, “Secukinumab”

Table 65: Clinical trial registry hand-searching strategy

Name of resource	Website	Date of search	Description of search	Keywords searched
Clinicaltrials.gov	https://classic.clinicaltrials.gov/	3rd November 2023	In advanced search: enter keyword in condition or disease box >> filter study type to “interventional studies (clinical trials) >> filter age group to “adult” and “older adult”>> filter last update posted from 04/01/2023 to date of hand search (11/03/2023)	“Hidradenitis suppurativa”
WHO ICTRP	https://trialsearch.who.int/AdvSearch.aspx	3rd November 2023	In advanced search: enter keyword in the title box >> filter recruitment status to “ALL” >> filter phases to “Phase 2”, “Phase 4”, and “Phase 4”,	“Hidradenitis suppurativa”

Abbreviations: WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

Table 66: Grey literature hand-searching strategy

Name of resource	Website	Date of search	Description of search	Keywords searched
U.S. Food & Drug administration	https://www.fda.gov/	3rd November 2023	Click 'search' in the top right-hand corner >> enter keyword into the search bar >> filter topic area to drugs	"Adalimumab", "Bimekizumab", "Secukinumab"
European Medicines Agency	https://www.ema.europa.eu/en	9th November 2023	Click the "medicines" dropdown menu and select "search" >> Enter the keyword into the search bar >> filter for "human" results under categories and "European public assessment reports (EPAR)" under medicine.	"Adalimumab", "Bimekizumab", "Secukinumab"

Table 67: Conference hand-searching strategy

Name of resource	Date of search	Year of conference	Website	Description of search	Keywords searched
ISPOR	20th November 2023	2023	https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-2023	Click “posters” in the “program” drop down >> search key word for each poster session.	Etanercept, Apremilast, Infliximab, SAR442970, Certolizumab, Golimumab, TNF, INCB054707, PF-06700841, PF06700841, Upadacitinib, Povorcitinib, Baricitinib, Tofacitinib, PF-06826647, PF06826647, Ruxolitinib, Oclacitinib, Peficitinib, Fedratinib, Filgotinib, Abrocitinib, Pacritinib, Deucravacitinib, Ritlecitinib, Momelotinib, CJM112, Izokibep, Sonelokimab, Brodalumab, Ixekizumab, Ustekinumab, Placebo, Brepocitinib, JAK, IL-17
ISPOR	20th November 2023	2022	https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-2022	Click “posters” in the “program” drop down >> search key word for each poster session.	
ISPOR Europe	20th November 2023	2021	https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-europe-2021/program/posters/poster-detail/euro2021-3409/?searchQuery=hidradenitis	Click “posters” in the “program” drop down >> search key word for each poster session.	“Hidradenitis”
		2022	https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-europe-2022	Click “posters” in the “program” drop down >> search key word for each poster session.	
Symposium on Hidradenitis Suppurativa Advances	20th November 2023	2020	https://www.dropbox.com/s/1xurks8pqnwhuk5/2020%20Program.pdf?dl=0	Scroll through abstracts	N/A
		2021	https://www.dropbox.com/s/inkq6pqre45yktd/2021%20SHSA%20Program.pdf?dl=0		
		2022	https://www.dropbox.com/s/8y67rvw46fzpitd/SHSA%20GUIDE%202022.pdf?dl=0		

Name of resource	Date of search	Year of conference	Website	Description of search	Keywords searched
(SHSA)					
		2023	https://team.joynadmin.org/documents/1070/651c7ce405973d19b87062f2.pdf		
European Hidradenitis Suppurativa Foundation (EHSF)	20th November 2023	2021	https://onlinelibrary.wiley.com/doi/pdfdirect/10.1111/exd.14342	Search “10th EHSF abstract book” >> click Pubmed link>> Open PDF via free full text link	“Etanercept”, “Apremilast”, “Infliximab”, “SAR442970”, “Certolizumab”, “Golimumab”, “INCB054707”, “PF-06700841”, “PF06700841”, “Upadacitinib”, “Povorcitinib”, “Baricitinib”, “Tofacitinib”, “PF-06826647”, “Ruxolitinib”, “Oclacitinib”, “Peficitinib”, “Fedratinib”, “Filgotinib”, “Abrocitinib”, “Pacritinib”, “Deucravacitinib”, “Ritlecitinib”, “Momelotinib”, “CJM112”, “Izokibep”, “Sonelokimab”, “Brodalumab”, “Ixekizumab”, “Ustekinumab”, “Brepocitinib”
		2022	https://onlinelibrary.wiley.com/doi/epdf/10.1111/exd.14557	Search “11th EHSF abstract book” >> click Pubmed link>> Open PDF via free full text link	
		2023	https://onlinelibrary.wiley.com/doi/epdf/10.1111/exd.14898	Search “12th EHSF abstract book” >> click Pubmed link>> Open PDF via free full text link	
European Acacemy of Dermatology and Venereology (EADV)	16th November 2023	2022 (symposium)	https://eadv.org/scientific/abstract-books/	EADV Symposium 2022 >> Acne and related disorders, hidradenitis suppurativa >> CTRL F keywords	“Etanercept”, “Apremilast”, “Infliximab”, “SAR442970”, “Certolizumab”, “Golimumab”, “INCB054707”, “PF-06700841”, “PF06700841”, “Upadacitinib”, “Povorcitinib”, “Baricitinib”, “Tofacitinib”, “PF-06826647”, “Ruxolitinib”, “Oclacitinib”, “Peficitinib”, “Fedratinib”, “Filgotinib”, “Abrocitinib”, “Pacritinib”, “Deucravacitinib”, “Ritlecitinib”, “Momelotinib”, “CJM112”, “Izokibep”, “Sonelokimab”, “Brodalumab”, “Ixekizumab”, “Ustekinumab”, “Brepocitinib”
		2022 (congress)	https://eadv.org/scientific/abstract-books/	EADV Congress 2022 >> Acne and related disorders, hidradenitis suppurativa >> CTRL F keywords	
		2023 (symposium)	https://eadv.org/scientific/abstract-books/	EADV Symposium 2023 >> Acne and related disorders, hidradenitis suppurativa >> CTRL F keywords	

Name of resource	Date of search	Year of conference	Website	Description of search	Keywords searched
		2023 (congress)	https://eadv.org/scientific/abstract-books/	EADV Congress 2023 >> Acne and related disorders, hidradenitis suppurativa >> CTRL F keywords	
American Academy of Dermatology (AAD)	21st November 2023	2020	https://conferences.medicom-publishers.com/wp-content/uploads/2021/07/E_MCR-AAD-2020.pdf	Ctrl F keyword on each page	"Hidradenitis"
		2021	https://www.jaad.org/issue/S0190-9622(21)X0013-8?pageStart=0	Search "AAD 2022 abstracts" >> Click the "List of issues" link (https://www.jaad.org/issues) >> Click 2021 Volume 85 >> Click Supplement - Issue 3 September 2021AB1-AB302 >> Ctrl F keyword on each page	"Hidradenitis"
		2022	https://www.jaad.org/issue/S0190-9622(22)X0004-2	Search "AAD 2022 abstracts" >> Click the "List of issues" link (https://www.jaad.org/issues) >> Click 2022 Volume 87 >> Click Volume 87, Issue 3, Supplement AB1-AB338 >> Ctrl F keyword on each page	"Hidradenitis"
		2023	https://eposters.aad.org/	Search "AAD 2023" >> Click the "session handouts" link under the first search result >> click the "VMX and Annual Meeting posters" link under "Poster exhibits" Click "search" in the top right hand corner >> search abstracts using keywords	"Etanercept", "Apremilast", "Infliximab", "SAR442970", "Certolizumab", "Golimumab", "INCB054707", "PF-06700841", "PF06700841", "Upadacitinib", "Povorcitinib", "Baricitinib", "Tofacitinib", "PF-06826647", "Ruxolitinib", "Oclacitinib", "Peficitinib", "Fedratinib", "Filgotinib", "Abrocitinib", "Pacritinib",

Name of resource	Date of search	Year of conference	Website	Description of search	Keywords searched
					"Deucravacitinib", "Ritlecitinib", "Momelotinib", "CJM112", "Izokibep", "Sonelokimab", "Brodalumab", "Ixekizumab", "Ustekinumab", "Brepocitinib"

Abbreviations: ISPOR, Professional Society for Health Economics and Outcomes Research.

Table 68: Clinical trial registry hand-searching strategy

Name of resource	Website	Date of search	Description of search	Keywords searched
Clinicaltrials.gov	https://classic.clinicaltrials.gov/	16th November 2023	In advanced search: enter keyword in condition or disease box >> filter study type to "interventional studies (clinical trials) and filter age group to "adult" and "older adult"	"Hidradenitis suppurativa"
WHO ICTRP	https://trialsearch.who.int/AdvSearch.aspx	16th November 2023	In advanced search: enter keyword in the title box >> filter recruitment status to "ALL" >> filter phases to "Phase 2", "Phase 3", and "Phase 4"	"Hidradenitis suppurativa"

Abbreviations: WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

Table 69: Grey literature hand-searching strategy

Name of resource	Website	Date of search	Description of search	Keywords searched
U.S. Food & Drug administration	https://www.fda.gov/	3rd November 2023	Click 'search' in the top right-hand corner >> enter keyword into the search bar >> filter topic area to drugs	"Etanercept", "Apremilast", "Infliximab", "SAR442970", "Certolizumab", "Golimumab", "INCB054707", "PF-06700841", "PF06700841", "Upadacitinib", "Povorcitinib", "Baricitinib", "Tofacitinib", "PF-06826647", "Ruxolitinib", "Oclacitinib", "Peficitinib", "Fedratinib", "Filgotinib", "Abrocitinib", "Pacritinib", "Deucravacitinib", "Ritlecitinib", "Momelotinib", "CJM112", "Izokibep", "Sonelokimab", "Brodalumab", "Ixekizumab", "Ustekinumab", "Brepocitinib"
European Medicines Agency	https://www.ema.europa.eu/en	9th November 2023	Click the "medicines" dropdown menu and select "search" >> Enter the keyword into the search bar >> filter for "human" results under categories and "European public assessment reports (EPAR)" under medicine.	"Etanercept", "Apremilast", "Infliximab", "SAR442970", "Certolizumab", "Golimumab", "INCB054707", "PF-06700841", "PF06700841", "Upadacitinib", "Povorcitinib", "Baricitinib", "Tofacitinib", "PF-06826647", "Ruxolitinib", "Oclacitinib", "Peficitinib" "Fedratinib", "Filgotinib", "Abrocitinib", "Pacritinib", "Deucravacitinib" "Ritlecitinib", "Momelotinib", "CJM112", "Izokibep", "Sonelokimab", "Brodalumab", "Ixekizumab", "Ustekinumab", "Brepocitinib"

C3. Please clarify if validated study design search filters were used within the search strategies presented in Table 77, 78, 79, 80, and provide references for the search filters where available.

The April 2023 SLR Embase search string (Table 77) for study design includes all terms of the validated filter for RCTs found on SIGN (Reference: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.sign.ac.uk%2Fassets%2Fsearch-filters-randomised-controlled-trials.docx&wdOrigin=BROWSELINK), with the addition of broader terms, to increase sensitivity (in particular, to ensure the search retrieved reports of open-label extension analyses of RCTs). The MEDLINE search string (Table 79) for study design includes all terms of the above validated filter for RCTs adapted for the MEDLINE database, found in the above link, with the addition of broader search terms for the same purpose. The CENTRAL search did not include this filter as it did not include any design terms.

The Embase and MEDLINE search strategies for the October 2023 clinical SLR (Tables 78 and 80, respectively) featured a randomised controlled trial (RCT) filter, modified from the Scottish Intercollegiate Guidelines Network (SIGN) (Scottish Intercollegiate Guidelines Network (SIGN). Methodology: Search filters. Available at: https://www.sign.ac.uk/what-we-do/methodology/search-filters/).

C4. Search strategies for the initial searches of cost-effectiveness and cost and healthcare resource use, carried out in May/June 2023, are missing (described on page 275, Section G.1.1, Appendix G). Likewise, search strategies for the original searches of HRQoL evidence, carried out in 2021, and the 1st update searches carried out in May 2023, are missing (described on page 294, Section H.1.1, Appendix H). Please provide all of these.

The search strings for the April 2023 cost-effectiveness, cost and healthcare resource use, and HRQoL SLRs, as well as the original 2021 HRQoL search strings are provided below.

Table 70. Search strategy for the April 2023 cost-effectiveness and HCRU and cost systematic reviews: Embase 1974 to June 7 2023

#	Searches	Results
1	acne invers$1.ti,ab.	544
2	invers$ acne.ti,ab.	15
3	hidradeniti$ suppurativ$.ti,ab.	6559
4	suppurativ$ hidradeniti$.ti,ab.	134
5	velpeau$ disease.ti,ab.	4
6	verneuil$ disease.ti,ab.	92

#	Searches	Results
7	exp suppurative hidradenitis/	7516
8	or/1-7	8006
9	exp Pharmacoeconomics/	230187
10	exp Socioeconomics/	1312021
11	exp Health economics/	1025594
12	Cost/	62525
13	exp Economic aspect/	2446873
14	(economic$ or cost$ or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expense or expenses or financial or finance or financed).ti,ab,kw.	1562192
15	exp economic model/	3730
16	exp Economics/	249148
17	exp Economic evaluation/	353727
18	"cost utility analysis"/	12258
19	Quality-Adjusted Life Year/	35313
20	(cost$ adj2 (comparison$ or effective$ or utilit$ or analys$ or benefit$ or minimi$ or outcome or outcomes)).ti,ab,kw.	304874
21	cost of illness.ab,ti,kw.	4693
22	"cost of illness"/	21189
23	"cost minimization analysis"/	3987
24	"cost effectiveness analysis"/	180768
25	"cost benefit analysis"/	94083
26	(cba or cea or cua or cma or cca).ti,ab,kw.	80610
27	(quality adjusted or adjusted life year$ or QALY$).ti,ab,kw.	40400
28	(ICER$ or incremental cost-effectiveness ratio$).ti,ab,kw.	21588
29	"cost control"/	76130
30	exp Budget/	33736
31	budget$.ti,ab,kw.	47262
32	Markov$.ti,ab,kw.	40971
33	Monte Carlo.ti,ab,kw.	61784
34	(decision$ adj2 (tree$ or analys$ or model$)).ti,ab,kw.	48903
35	(partition$ survival or PSM or PartSA).ti,ab,kw.	12680
36	exp Monte Carlo method/	52108
37	exp "Decision tree"/	21548
38	Microsimulation.ti,ab,kw.	2711
39	discrete event simulation.ti,ab,kw.	1452
40	patient level simulation.ti,ab,kw.	245
41	Simulation/	252595
42	(expenditure$ not energy).ti,ab,kw.	50511
43	(value adj1 money).ti,ab,kw.	45

#	Searches	Results
44	exp "Health care cost"/	337648
45	Hospitalization cost/	9996
46	Nursing cost/	208
47	"Drug cost"/	85587
48	exp Resource allocation/	24862
49	Resource management/	11815
50	((healthcare or health care or resourc$ or service$ or hospital$) adj2 (utili$ or us$)).ti,ab,kw.	275561
51	"Length of stay"/	267328
52	((length or duration or extended or prolonged) adj stay).ti,ab,kw.	2211
53	Health care utilization/	93723
54	exp Absenteeism/	19865
55	absenteeism.ti,ab,kw.	10713
56	((medical or sick) adj leave).ti,ab,kw.	8137
57	exp Unemployment/	27349
58	exp Employment/	124912
59	exp Work capacity/	13660
60	exp Employment status/	46879
61	exp Work disability/	5759
62	(employment or unemployment or unemployed or employability or employable or unemployable).ti,ab,kw.	120363
63	(work capacit$ or work status or work activit$).ti,ab,kw.	11886
64	poverty/ or extreme poverty/	55195
65	poverty.ti,ab,kw.	39986
66	social deprivation.ti,ab,kw.	3221
67	exp Income/	130950
68	income.ti,ab,kw.	215663
69	social impact.ti,ab,kw.	4103
70	exp Medical leave/	8667
71	exp Social Isolation/	32338
72	exp Disability/	190524
73	(disability or disable$ or disabilities).ti,ab,kw.	369163
74	Productivity/	50455
75	((productivity or efficiency) adj3 (loss or losing or reduc$ or restrict$)).ti,ab,kw.	31682
76	((direct or indirect) adj cost$).mp.	22843
77	caregiver burden/ or caregiver/ or caregiver support/	122999
78	(caregiver$ adj3 (burden or support or cost$)).mp.	24304
79	"societal cost"/	352
80	(societal adj (cost$ or impact$ or value)).mp.	5659

#	Searches	Results
81	or/9-80	4722464
82	8 and 81	956
83	exp animal/ not exp human/	5188297
84	(editorial or note or case reports).pt.	1722422
85	82 not 83	954
86	85 not 84	915
87	limit 86 to english language	898
88	limit 87 to conference abstract status	300
89	limit 88 to yr="2021 - Current"	115
90	87 not (88 not 89)	713
91	limit 90 to yr="2012 -Current"	**651**

Table 71. Search strategy for the April 2023 cost-effectiveness and HCRU and cost systematic reviews: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to June 7, 2023

#	Searches	Results
1	acne invers$1.ti,ab.	316
2	invers$ acne.ti,ab.	9
3	hidradeniti$ suppurativ$.ti,ab.	3971
4	suppurativ$ hidradeniti$.ti,ab.	83
5	velpeau$ disease.ti,ab.	1
6	verneuil$ disease.ti,ab.	58
7	exp Hidradenitis Suppurativa/	3097
8	or/1-7	4315
9	Economics/	27502
10	exp Economics, Pharmaceutical/	3105
11	exp Economics, Medical/	14393
12	exp Economics, hospital/	25715
13	Economics, nursing/	4013
14	Economics, Pharmaceutical/	3105
15	exp Socioeconomic Factors/	509794
16	exp "Costs and Cost Analysis"/	264675
17	exp Models, Economic/	16214
18	exp resource allocation/	18917
19	Economics, Dental/	1921
20	(economic$ or cost$ or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expense or expenses or financial or finance or financed).ti,ab,kf.	1205510
21	Cost allocation/	2018

#	Searches	Results
22	Cost control/	21665
23	Cost savings/	12713
24	"Cost of Illness"/	31502
25	cost of illness.ab,ti,kf.	2763
26	quality-adjusted life years/	15660
27	(cost$ adj2 (comparison$ or effective$ or utilit$ or analys$ or benefit$ or minimi$ or outcome or outcomes)).ti,ab,kf.	222024
28	Disability-Adjusted Life Years/	182
29	Cost-Benefit Analysis/	92497
30	(ICER$ or incremental cost-effectiveness ratio$).ti,ab,kf.	12264
31	(quality adjusted or adjusted life year$ or QALY$).ti,ab,kf.	25221
32	cost-effectiveness analysis/	322
33	(cba or cea or cua or cma or cca).ti,ab,kf.	55263
34	exp "Fees and Charges"/	31368
35	exp Budgets/	14108
36	Direct service costs/	1217
37	Drug costs/	17390
38	Health expenditures/	23963
39	budget$.ti,ab,kf.	35832
40	(value adj2 (money or monetary)).ti,ab,kf.	3021
41	economic model$.ti,ab,kf.	4565
42	Markov chains/	15958
43	Monte Carlo method/	32168
44	Decision tree/	12084
45	exp Decision theory/	13242
46	Markov$.ti,ab,kf.	32324
47	Monte Carlo.ti,ab,kf.	59790
48	(decision$ adj2 (tree$ or analys$ or model$)).ti,ab,kf.	35944
49	(partition$ survival or PSM or PartSA).ti,ab,kf.	8286
50	microsimulation.ti,ab,kf.	1794
51	simulation.ti,ab,kf.	269099
52	(expenditure$ not energy).ti,ab,kf.	37290
53	exp Health Care Costs/	71835
54	exp Hospital Costs/	11947
55	exp Health Resources/	28997
56	Health Services/	27585
57	exp Drug Utilization/	28119
58	((healthcare or health care or resourc$ or service$ or hospital$) adj2 (utili$ or us$)).ti,ab,kf.	175794

#	Searches	Results
59	((length or duration or extended or prolonged) adj stay).ti,ab,kf.	1249
60	"Length of Stay"/	102244
61	exp Absenteeism/	9760
62	Presenteeism/	583
63	absenteeism.ti,ab,kf.	7381
64	exp Sick Leave/	6739
65	((medical or sick) adj leave).ti,ab,kf.	6645
66	presenteeism.ti,ab,kf.	1848
67	exp Unemployment/	7770
68	(employment or unemploy$ or employability or employable).ti,ab,kf.	91021
69	exp Employment/	99632
70	(work capacity or work status or work activity).ti,ab,kf.	8182
71	Poverty/	43643
72	poverty areas/	6651
73	poverty.ti,ab,kf.	33873
74	socioeconomic.ti,ab,kf.	127700
75	social deprivation.ti,ab,kf.	2239
76	exp Income/	70570
77	income.ti,ab,kf.	174539
78	((productivity or efficiency) adj3 (loss or losing or reduc$ or restrict$)).ti,ab,kf.	25149
79	((direct or indirect) adj cost$).mp.	13392
80	social impact.ti,ab,kf.	2956
81	exp Social Isolation/	25457
82	(disability or disable$ or disabilities).ti,ab,kf.	261899
83	exp Caregivers/	49748
84	(caregiver$ adj3 (burden or support or cost$)).mp.	12043
85	(societal adj (cost$ or impact$ or value)).mp.	4088
86	or/9-85	2861192
87	8 and 86	262
88	exp Animals/ not exp Humans/	5127681
89	(case reports or editorial).pt.	2989361
90	87 not 88	261
91	90 not 89	241
92	limit 91 to english language	230
93	limit 92 to yr="2012 -Current"	**207**

Table 72. Search strategy for the April 2023 cost-effectiveness and HCRU and cost systematic reviews: Econlit 1886 to June 1, 2023

#	Searches	Results
1	acne invers*.mp.	0
2	invers* acne.mp.	0
3	hidradeniti* suppurativ*.mp.	1
4	suppurativ* hidradeniti*.mp.	0
5	velpeau* disease.mp.	0
6	verneuil* disease.mp.	0
7	or/1-6	**1**

Table 73. Search strategy for the April 2023 cost-effectiveness and HCRU and cost systematic reviews: EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016

#	Searches	Results
1	acne invers*.mp.	0
2	invers* acne.mp.	0
3	hidradeniti* suppurativ*.mp.	0
4	suppurativ* hidradeniti*.mp.	0
5	velpeau* disease.mp.	0
6	verneuil* disease.mp.	0
7	exp Hidradenitis Suppurativa/	0
8	or/1-7	**0**

Table 74. Search strategy for the April 2023 cost-effectiveness and HCRU and cost systematic reviews: EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016

#	Searches	Results
1	acne invers*.mp.	0
2	invers* acne.mp.	0
3	hidradeniti* suppurativ*.mp.	2
4	suppurativ* hidradeniti*.mp.	0
5	velpeau* disease.mp.	0
6	verneuil* disease.mp.	0
7	or/1-6	**2**

Table 75. Search strategy for the April 2023 cost-effectiveness and HCRU and cost systematic reviews: EBM Reviews - Health Technology Assessment 4th Quarter 2016

#	Searches	Results
1	acne invers*.mp.	0
2	invers* acne.mp.	0
3	hidradeniti* suppurativ*.mp.	1
4	suppurativ* hidradeniti*.mp.	0
5	velpeau* disease.mp.	0
6	verneuil* disease.mp.	0
7	exp Hidradenitis Suppurativa/	1
8	or/1-7	**1**

Please find further details of the methods and results of the SLRs undertaken in 2021 and 2023 contained within the respective confidential appendices supplied [24-26].

Table *76*: Embase search strategy for the 2021 HRQoL SLR run on 29 August 2021

#	Searches	Results
1	exp *suppurative hidradenitis/	4073
2	Hidradenitis suppurativa.ti,ab,kw.	4813
3	acne inversa.ti,ab,kw.	643
4	or/1-3	5106
5	patient$ perspective$.tw.	16296
6	patient$ preference$.tw.	20006
7	daily activit$.tw.	29162
8	(activit$ of daily living or activit$ of daily life).tw.	46386
9	patient$ reported symptom$.tw.	3253
10	patient$ reported outcome$.tw.	39483
11	PRO.tw.	324390
12	survey.tw.	744220
13	scale.tw.	1078152
14	diar$.tw.	221581
15	self-report$.tw.	228076
16	function$ status.tw.	41929
17	questionnaire$.tw.	821212
18	psychometric.tw.	57985
19	instrument$.tw.	392289
20	measure$.tw.	4551898
21	interview$.tw.	496056
22	focus group$.tw.	66326

#	Searches	Results
23	quality of life.tw.	491148
24	QOL.tw.	81772
25	health-related quality of life.tw.	70968
26	HRQL.tw.	6354
27	HRQoL.tw.	30424
28	satisfaction.tw.	210910
29	well being.tw.	108512
30	emotional.tw.	227684
31	(cope or coping).tw.	117794
32	patient-reported.tw.	71600
33	fatigue.tw.	167742
34	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	10458
35	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or shortform thirtysix or short form thirtysix).tw.	44664
36	(EQ-5D or EuroQol-5D or EQ 5D or EuroQol 5D).tw.	19485
37	((work productivity adj2 activity impairment) or WPAI).tw.	2470
38	clinical outcome/	192957
39	(clinician reported or clinician-reported).tw.	1047
40	((care giver or care-giver or caregiver) adj reported).mp.	1166
41	clinical outcome$ assessment$.mp.	785
42	(clinro or COA or PRO).mp.	407384
43	outcome assessment/ or patient-reported outcome/	627726
44	questionnaire/ or "quality of life"/	1180789
45	DLQI.ti,ab,kw.	3910
46	dermatology life quality index.ti,ab,kw.	3896
47	mental health/	157283
48	numeric rating scale/	10898
49	social interaction/	60761
50	sexual health/	17799
51	visual analog scale/	98849
52	patient global impression of severity/	17
53	itch.tw.	9300
54	(Treatment Satisfaction Questionnaire for Medication or TSQM-9).tw.	592
55	(Patient Health Questionnaire-9 or PHQ- 9).tw.	9499
56	(Columbia-Suicide Severity Rating Scale or C-SSRS).tw.	617
57	physician$ global assessment$.tw.	4995
58	patient$ global assessment$.tw.	3695
59	or/5-58	8571391
60	4 and 59	1793
61	limit 60 to (english language and yr="2000-current")	1723
62	limit 61 to (conference abstract or conference paper or "conference review" or editorial or erratum or letter or note)	914

#	Searches	Results
63	61 not 62	809

Table 77: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) search strategy for the 2021 HRQoL SLR run on 29 August 2021

#	Searches	Results
1	exp Hidradenitis Suppurativa/	2352
2	Hidradenitis suppurativa.mp.	3405
3	acne inversa/	2352
4	acne inversa.ti,ab,kw.	425
5	or/1-4	3441
6	patient$ perspective$.tw.	10724
7	patient$ preference$.tw.	12809
8	daily activit$.tw.	19090
9	(activit$ of daily living or activit$ of daily life).tw.	32446
10	patient$ reported symptom$.tw.	1578
11	patient$ reported outcome$.tw.	22640
12	PRO.tw.	213505
13	survey.tw.	578680
14	scale.tw.	807711
15	diar$.tw.	150981
16	self-report$.tw.	173650
17	function$ status.tw.	27629
18	questionnaire$.tw.	566627
19	psychometric.tw.	47888
20	instrument$.tw.	304398
21	measure$.tw.	3538277
22	interview$.tw.	391589
23	focus group$.tw.	52908
24	quality of life.tw.	310540
25	QOL.tw.	43136
26	health-related quality of life.tw.	48896
27	HRQL.tw.	3706
28	HRQoL.tw.	18575
29	satisfaction.tw.	150399
30	well being.tw.	87766
31	emotional.tw.	169770
32	(cope or coping).tw.	92300
33	patient-reported.tw.	39465

#	Searches	Results
34	fatigue.tw.	103974
35	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	6503
36	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or shortform thirtysix or short form thirtysix).tw.	27496
37	(EQ-5D or EuroQol-5D or EQ 5D or EuroQol 5D).tw.	10434
38	((work productivity adj2 activity impairment) or WPAI).tw.	744
39	clinical outcome$ assessment$.tw.	360
40	(clinician reported or clinician-reported).tw.	549
41	((care giver or care-giver or caregiver) adj reported).mp.	826
42	clinical outcome$ assessment$.mp.	409
43	(clinro or COA or PRO).mp.	310448
44	outcome assessment/ or patient-reported outcome/	9297
45	questionnaire/ or "quality of life"/	668157
46	DLQI.ti,ab,kw.	1707
47	dermatology life quality index.ti,ab,kw.	2088
48	Pain Measurement/	90494
49	numeric rating scale.tw.	4435
50	Mental Health/	46415
51	(visual analogue scale$ or VAS).ti,ab,kw.	66910
52	Sexual Health/	1570
53	Social Interaction/	708
54	patient global impression of severity.mp.	58
55	itch.tw.	5550
56	(Treatment Satisfaction Questionnaire for Medication or TSQM-9).tw.	230
57	(Patient Health Questionnaire-9 or PHQ- 9).tw.	5716
58	(Columbia-Suicide Severity Rating Scale or C-SSRS).tw.	277
59	physician$ global assessment$.tw.	2007
60	patient$ global assessment$.tw.	1654
61	or/6-60	6207367
62	5 and 61	805
63	limit 62 to english language	769
64	limit 63 to yr="2010- Current"	700
65	limit 64 to (comment or editorial or lecture or letter)	66
66	64 not 65	634

Table 78: APA PsycInfo search strategy for the 2021 HRQoL SLR run to August Week 2 2021

#	Searches	Results
1	hidradenitis suppurativa.ti,ab.	8
2	acne inversa.ti,ab.	1
3	1 or 2	8
4	limit 3 to english language	6
5	limit 4 to yr="2010 -Current"	6

Table 79: Combined search strategy for the 2021 HRQoL SLR

#	Searches	Results
1	exp *suppurative hidradenitis/	6324
2	Hidradenitis suppurativa.ti,ab,kw.	8001
3	acne inversa.ti,ab,kw.	1068
4	or/1-3	8513
5	patient$ perspective$.tw.	30396
6	patient$ preference$.tw.	35626
7	daily activit$.tw.	54464
8	(activit$ of daily living or activit$ of daily life).tw.	90311
9	patient$ reported symptom$.tw.	5019
10	patient$ reported outcome$.tw.	65361
11	PRO.tw.	557485
12	survey.tw.	1578535
13	scale.tw.	2215606
14	diar$.tw.	389152
15	self-report$.tw.	537240
16	function$ status.tw.	74682
17	questionnaire$.tw.	1679079
18	psychometric.tw.	160600
19	instrument$.tw.	839448
20	measure$.tw.	8874497
21	interview$.tw.	1235552
22	focus group$.tw.	158934
23	quality of life.tw.	880038
24	QOL.tw.	136285
25	health-related quality of life.tw.	132387
26	HRQL.tw.	11076
27	HRQoL.tw.	54396
28	satisfaction.tw.	476982

#	Searches	Results
29	well being.tw.	290408
30	emotional.tw.	634606
31	(cope or coping).tw.	315397
32	patient-reported.tw.	116552
33	fatigue.tw.	295889
34	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	18554
35	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or shortform thirtysix or short form thirtysix).tw.	77801
36	(EQ-5D or EuroQol-5D or EQ 5D or EuroQol 5D).tw.	32164
37	((work productivity adj2 activity impairment) or WPAI).tw.	3328
38	clinical outcome/	194251
39	(clinician reported or clinician-reported).tw.	1767
40	((care giver or care-giver or caregiver) adj reported).mp.	2490
41	clinical outcome$ assessment$.mp.	1275
42	(clinro or COA or PRO).mp.	738707
43	outcome assessment/ or patient-reported outcome/	638916
44	questionnaire/ or "quality of life"/	1915304
45	DLQI.ti,ab,kw.	5684
46	dermatology life quality index.ti,ab,kw.	6067
47	mental health/	276105
48	numeric rating scale/	10968
49	social interaction/	86545
50	sexual health/	22123
51	visual analog scale/	102910
52	patient global impression of severity/	17
53	itch.tw.	15374
54	(Treatment Satisfaction Questionnaire for Medication or TSQM-9).tw.	848
55	(Patient Health Questionnaire-9 or PHQ- 9).tw.	18234
56	(Columbia-Suicide Severity Rating Scale or C-SSRS).tw.	1102
57	physician$ global assessment$.tw.	7037
58	patient$ global assessment$.tw.	5430
59	or/5-58	16710271
60	4 and 59	2600
61	limit 60 to (english language and yr="2000-current")	2474
62	limit 61 to (conference abstract or conference paper or "conference review" or editorial or erratum or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher,APA PsycInfo; records were retained]	972
63	61 not 62	1502

#	Searches	Results
64	63 use oemezd	812
65	exp Hidradenitis Suppurativa/	7820
66	Hidradenitis suppurativa.mp.	8266
67	acne inversa/	2474
68	acne inversa.ti,ab,kw.	1068
69	or/65-68	9320
70	patient$ perspective$.tw.	30396
71	patient$ preference$.tw.	35626
72	daily activit$.tw.	54464
73	(activit$ of daily living or activit$ of daily life).tw.	90311
74	patient$ reported symptom$.tw.	5019
75	patient$ reported outcome$.tw.	65361
76	PRO.tw.	557485
77	survey.tw.	1578535
78	scale.tw.	2215606
79	diar$.tw.	389152
80	self-report$.tw.	537240
81	function$ status.tw.	74682
82	questionnaire$.tw.	1679079
83	psychometric.tw.	160600
84	instrument$.tw.	839448
85	measure$.tw.	8874497
86	interview$.tw.	1235552
87	focus group$.tw.	158934
88	quality of life.tw.	880038
89	QOL.tw.	136285
90	health-related quality of life.tw.	132387
91	HRQL.tw.	11076
92	HRQoL.tw.	54396
93	satisfaction.tw.	476982
94	well being.tw.	290408
95	emotional.tw.	634606
96	(cope or coping).tw.	315397
97	patient-reported.tw.	116552
98	fatigue.tw.	295889
99	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	18554
100	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or shortform thirtysix or short form thirtysix).tw.	77801

#	Searches	Results
101	(EQ-5D or EuroQol-5D or EQ 5D or EuroQol 5D).tw.	32164
102	((work productivity adj2 activity impairment) or WPAI).tw.	3328
103	clinical outcome$ assessment$.tw.	1176
104	(clinician reported or clinician-reported).tw.	1767
105	((care giver or care-giver or caregiver) adj reported).mp.	2490
106	clinical outcome$ assessment$.mp.	1275
107	(clinro or COA or PRO).mp.	738707
108	outcome assessment/ or patient-reported outcome/	638916
109	questionnaire/ or "quality of life"/	1915304
110	DLQI.ti,ab,kw.	5684
111	dermatology life quality index.ti,ab,kw.	6067
112	Pain Measurement/	102343
113	numeric rating scale.tw.	11863
114	Mental Health/	276105
115	(visual analogue scale$ or VAS).ti,ab,kw.	180339
116	Sexual Health/	22123
117	Social Interaction/	86545
118	patient global impression of severity.mp.	263
119	itch.tw.	15374
120	(Treatment Satisfaction Questionnaire for Medication or TSQM-9).tw.	848
121	(Patient Health Questionnaire-9 or PHQ- 9).tw.	18234
122	(Columbia-Suicide Severity Rating Scale or C-SSRS).tw.	1102
123	physician$ global assessment$.tw.	7037
124	patient$ global assessment$.tw.	5430
125	or/70-124	16660230
126	69 and 125	2667
127	limit 126 to english language	2576
128	limit 127 to yr="2010- Current"	2396
129	limit 128 to (comment or editorial or lecture or letter) [Limit not valid in Embase,APA PsycInfo; records were retained]	192
130	128 not 129	2204
131	130 use ppezv	637
132	64 or 131	1449
133	remove duplicates from 132	875

Table *80*: Embase search strategy for the 2023 HRQoL SLR update run on 07 June 2023 (covers period from 01 August 2021 up to 15 May 2023)

#	Searches	Results
1	exp *suppurative hidradenitis/	5647
2	Hidradenitis suppurativa.ti,ab,kw.	6648
3	acne inversa.ti,ab,kw.	851
4	or/1-3	6986
5	patient$ perspective$.tw.	20204
6	patient$ preference$.tw.	23852
7	daily activit$.tw.	34183
8	(activit$ of daily living or activit$ of daily life).tw.	53889
9	patient$ reported symptom$.tw.	4157
10	patient$ reported outcome$.tw.	56003
11	PRO.tw.	382622
12	survey.tw.	881076
13	scale.tw.	1290831
14	diar$.tw.	249658
15	self-report$.tw.	271205
16	function$ status.tw.	47985
17	questionnaire$.tw.	960763
18	psychometric.tw.	67354
19	instrument$.tw.	442729
20	measure$.tw.	5126864
21	interview$.tw.	573476
22	focus group$.tw.	79326
23	quality of life.tw.	588593
24	QOL.tw.	98079
25	health-related quality of life.tw.	84909
26	HRQL.tw.	7088
27	HRQoL.tw.	37094
28	satisfaction.tw.	249708
29	well being.tw.	133862
30	emotional.tw.	267232
31	(cope or coping).tw.	137795
32	patient-reported.tw.	96676
33	fatigue.tw.	198672
34	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	12261
35	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or shortform thirtysix or short form thirtysix).tw.	49908

#	Searches	Results
36	(EQ-5D or EuroQol-5D or EQ 5D or EuroQol 5D).tw.	24581
37	((work productivity adj2 activity impairment) or WPAI).tw.	3042
38	clinical outcome/	309154
39	(clinician reported or clinician-reported).tw.	1491
40	((care giver or care-giver or caregiver) adj reported).mp.	1668
41	clinical outcome$ assessment$.mp.	1061
42	(clinro or COA or PRO).mp.	481198
43	outcome assessment/ or patient-reported outcome/	882425
44	questionnaire/ or "quality of life"/	1390843
45	DLQI.ti,ab,kw.	5048
46	dermatology life quality index.ti,ab,kw.	5056
47	mental health/	204535
48	numeric rating scale/	18177
49	social interaction/	71442
50	sexual health/	21395
51	visual analog scale/	122936
52	patient global impression of severity/	29
53	itch.tw.	11414
54	(Treatment Satisfaction Questionnaire for Medication or TSQM-9).tw.	736
55	(Patient Health Questionnaire-9 or PHQ- 9).tw.	13796
56	(Columbia-Suicide Severity Rating Scale or C-SSRS).tw.	821
57	physician$ global assessment$.tw.	5896
58	patient$ global assessment$.tw.	4343
59	or/5-58	9957912
60	4 and 59	2606
61	limit 60 to english language	2545
62	limit 61 to (conference abstract or conference paper or "conference review" or editorial or erratum or letter or note)	1255
63	61 not 62	1290
64	limit 63 to dd=20210801-20230515	57
65	limit 63 to dc=20210801-20230515	407
66	limit 63 to rd=20210801-20230515	369
67	or/64-66	**426**

Table *81*: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) search strategies for the 2023 HRQoL SLR update run on 07, June 2023 (covers period from 01 August 2021 up to 15 May 2023)

#	Searches	Results
1	exp Hidradenitis Suppurativa/	3097
2	Hidradenitis suppurativa.mp.	4274
3	acne inversa/	3097
4	acne inversa.ti,ab,kw.	510
5	or/1-4	4314
6	patient$ perspective$.tw.	12928
7	patient$ preference$.tw.	14690
8	daily activit$.tw.	22233
9	(activit$ of daily living or activit$ of daily life).tw.	37468
10	patient$ reported symptom$.tw.	1956
11	patient$ reported outcome$.tw.	31717
12	PRO.tw.	246233
13	survey.tw.	676397
14	scale.tw.	956688
15	diar$.tw.	165595
16	self-report$.tw.	203249
17	function$ status.tw.	30745
18	questionnaire$.tw.	659482
19	psychometric.tw.	55744
20	instrument$.tw.	340249
21	measure$.tw.	3914864
22	interview$.tw.	450424
23	focus group$.tw.	63223
24	quality of life.tw.	367009
25	QOL.tw.	51460
26	health-related quality of life.tw.	57187
27	HRQL.tw.	4033
28	HRQoL.tw.	22245
29	satisfaction.tw.	177409
30	well being.tw.	109019
31	emotional.tw.	198722
32	(cope or coping).tw.	108245
33	patient-reported.tw.	52349

#	Searches	Results
34	fatigue.tw.	121242
35	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	7520
36	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or shortform thirtysix or short form thirtysix).tw.	30276
37	(EQ-5D or EuroQol-5D or EQ 5D or EuroQol 5D).tw.	13106
38	((work productivity adj2 activity impairment) or WPAI).tw.	968
39	clinical outcome$ assessment$.tw.	476
40	(clinician reported or clinician-reported).tw.	778
41	((care giver or care-giver or caregiver) adj reported).mp.	1104
42	clinical outcome$ assessment$.mp.	553
43	(clinro or COA or PRO).mp.	351044
44	outcome assessment/ or patient-reported outcome/	94941
45	questionnaire/ or "quality of life"/	761270
46	DLQI.ti,ab,kw.	2222
47	dermatology life quality index.ti,ab,kw.	2664
48	Pain Measurement/	94499
49	numeric rating scale.tw.	5653
50	Mental Health/	60800
51	(visual analogue scale$ or VAS).ti,ab,kw.	78011
52	Sexual Health/	2423
53	Social Interaction/	1529
54	patient global impression of severity.mp.	80
55	itch.tw.	6523
56	(Treatment Satisfaction Questionnaire for Medication or TSQM-9).tw.	298
57	(Patient Health Questionnaire-9 or PHQ- 9).tw.	8541
58	(Columbia-Suicide Severity Rating Scale or C-SSRS).tw.	384
59	physician$ global assessment$.tw.	2314
60	patient$ global assessment$.tw.	1882
61	or/6-60	7020642
62	5 and 61	1107
63	limit 62 to english language	1069
64	limit 63 to (comment or editorial or lecture or letter)	91
65	63 not 64	978
66	limit 65 to dt=20210801-20230515	282
67	limit 65 to rd=20210801-20230515	500
68	or/66-67	**509**

Table *82*: APA PsycInfo search strategy for the 2023 HRQoL SLR update run on 07 June 2023 (covers period from 2021 to May Week 5 2023)

#	Searches	Results
1	hidradenitis suppurativa.ti,ab.	12
2	acne inversa.ti,ab.	2
3	1 or 2	13
4	limit 3 to english language	10
5	limit 4 to yr="2021 -Current"	**3**

C5. Please provide the name of the interface used to search MEDLINE, Embase, and EconLit, which is missing from page 275, Section G.1.1, Appendix G, and from page 294, Section H.1.1, Appendix H.

All searches were conducted via OVID SP interface.

C6. Please provide the following details for the conference abstract searches on page 276, Section G.1.1, Appendix G, the website searches on page 275, Section G.1.1, Appendix G and the conference abstract searches on page 294, Section H.1.1, Appendix H:

a) The date that these searches were carried out

b) Search strategies used in each resource

Conference abstract searches for the economic SLR were conducted on June 18th to 19th 2023. Additionally, for the following two conferences, searches were conducted again on November 8th 2023 during the SLR update, because more recent sessions of these conferences had occurred since the de novo SLR: World congress of dermatology, American Academy of Dermatology Association.

Website searches were conducted on November 27th to 28th, 2023.

Conference abstract searches for the HRQoL SLR were conducted on June 15th to 16th 2023. Additionally, for the following two conferences, searches were conducted again on November 8th 2023 during the SLR update, because more recent sessions of these conferences had occurred: World congress of dermatology, American Academy of Dermatology Association.

Where a search engine field was available (e.g. ISPOR database), the disease term (hidradenitis) was used. Where no search engine field was available titles in the conference programmes' titles and abstracts were hand-searched.

Textual clarifications

C7. There appear to be a few discrepancies between Table 49 and Table 130 (e.g., the number of patients in the 'Initial and maintenance treatment period (weeks 0-48)' who had 'Infections and infestations', 'Fungal infections', Hypersensitivity reaction', 'Dermatitis and eczema', or 'Hepatic events'), please clarify why the discrepancies arise.

Table 49 is based on the ISS and Table 130 is based on study level data. Table 49 only includes events that occurred on Bimekizumab while Table 130 includes events that occurred on Placebo for the Placebo-Bimekizumab 320mg Q2W treatment groups.

C8. Could the company please check all confidentiality markings in Section B.2 and corresponding appendices. The extension trial results are marked as confidential; as these are not commercially sensitive data it is unclear whether they should they be. If confidentiality is required please give a clear explanation of the reasoning for this, as per NICE guidelines.

Clinical data from the extension trial is currently without a publication plan and is awaiting first public presentation at a congress scheduled to take place after documentation from NICE would be released to the public. As per the principles for marking and redacting confidential information in technology appraisals and highly specialised technologies evaluations '*Clinical data should be treated as clinical data without a publication plan if: there is clinical data awaiting first public presentation at a congress that is scheduled to take place after documentation from NICE would be released to the public, and this data is not awaiting publication in a journal or within marketing authorisation documentation'*. Thus, the extension data should remain marked as confidential.

Other points

C9. Please provide the full text for reference 75 in the submission (Lee et al. 2023)

Please see full text reference provided [27].

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EAG additional clarification question

B17.2. Priority: The base-case analysis assumes that response level on BSC is maintained beyond Week 48 of the model. This means that patients who discontinue active treatment (due to the TA935 all-cause discontinuation probability) and begin BSC are likely to maintain their response level indefinitely. This assumption appears to generate a significant proportion of incremental QALYs on BKZ/SEC vs BSC.

a) If the company intend to include a 'durable response' assumption on BSC in the model, please ensure that transition probabilities on BSC beyond Week 48 are applied only once a patient who has discontinued BKZ/SEC has been on BSC for 48 weeks, rather than from Week 48 of the model time horizon.

b) Please include a model scenario in which the RR for placebo vs bimekizumab is used to generate a BSC transition matrix for the maintenance phase. Please also apply these transition probabilities beyond Week 48 (i.e. combine CS Scenarios 3 and 7). Please comment on the plausibility of this scenario.

Unfortunately, it was not possible to implement the required changes to the cost-effectiveness model to address this additional clarification question in the timeframe given. This is because major model structural changes would have been required, including implementation of the additional tunnel states. Additionally, due to the complexity of these required changes, a full model validation assessment would also have been necessary to ensure results were consistent and changes were implemented correctly in the model.

In the submitted response to the original B17 clarification question provided, UCB presented an analysis that allows replication of PIONEER II up to week 36, while slowing long-term deterioration by applying a relative risk to the 9.6% probability per cycle of BSC patients becoming a non-responder from any state in the loss of response scenario. For the exploratory analysis, a relative risk of 0.1 is used after week 48 with the intention of having a greater number of patients exhibit durable

response on BSC without fixing response in the long-term. The exploratory analysis goes some way in exploring the impact of fixing the long-term response for patients on BSC.

With regards to the analysis that uses the RR derived from NMA of the 12/16-week data, as noted previously, the synthesis of this with the model baseline transition probabilities produced improving response estimates for patients on BSC in the long-term, which was contested by clinical experts.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bimekizumab for treating moderate to severe hidradenitis suppurativa [ID6134]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted] on behalf of the British Association of Dermatologists' Therapy & Guidelines sub-committee
2. Name of organisation	British Association of Dermatologists
3. Job title or position	Consultant Dermatologists
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes ~~or No~~ A specialist in the treatment of people with this condition? Yes ~~or No~~ A specialist in the clinical evidence base for this condition or technology? Yes ~~or No~~ Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training, and research of dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of dermatology services across all service settings. It is funded by the activities of its members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1) To treat skin inflammation in the form of inflammatory nodules, abscesses and skin tunnels which cause severe pain, pus production and odour, resulting in substantial reduction in quality of life. 2) Prevention of disease progression. This is important in hidradenitis suppurativa (HS) because it is a scarring condition. The scarring limits function, which in turn reduces ability to work and study. Reversal of scarring may require extensive surgery, for example axillary surgery healing times are about 3 months for wide excisions and may exceed 6 months for the groin and buttocks.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The current standard treatment response definition is HiSCR50, a trial endpoint defined as a 50% reduction from baseline in the sum of inflammatory nodules and abscesses, with no increase in abscesses or draining skin tunnels. A reduction of 4 points in the dermatology life quality index (DLQI) is also relevant, as well as a reduction in pain numerical rating scale (NRS).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – in the PIONEER studies for adalimumab, up until recently the only licensed treatment for HS, the HiSCR50 endpoint was reached by only 50% of trial participants. This means that only 50% of participants had a 50% reduction in their inflammatory lesions. As a consequence, many patients on adalimumab therapy still experience substantial morbidity from their active HS. In addition, secondary failure of adalimumab often occurs and so another biologic therapy option is greatly needed. The HS management pathway follows the BAD guidelines 2018 (https://onlinelibrary.wiley.com/doi/10.1111/bjd.17537) and we envisage bimekizumab (and recently licensed and NICE-approved secukinumab) to fit in the pathway immediately after adalimumab.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	As per the management pathway from the BAD guidelines 2018 (https://onlinelibrary.wiley.com/doi/10.1111/bjd.17537)

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	As above.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	As above.
9c. What impact would the technology have on the current pathway of care?	It would provide an alternative treatment option for patients who have not responded adequately to adalimumab, due to primary or secondary failure of adalimumab therapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – bimekizumab is already used for moderate-to-severe psoriasis in adults.
10a. How does healthcare resource use differ between the technology and current care?	Provision of bimekizumab and secukinumab would be in the same patient population treated by adalimumab, namely moderate-to severe HS. Failure of adalimumab therapy results in many patients needing additional therapy, which can include extensive surgery.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care.
10c. What investment is needed to introduce the technology? (For example,	No additional investment required as bimekizumab is already used for psoriasis.

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – at the moment, people with HS receiving insufficient benefit from adalimumab have no other treatment option except secukinumab.
11a. Do you expect the technology to increase length of life more than current care?	Difficult to quantify, however, HS is associated with reduced life expectancy. A Finnish study showed that people with HS on average live for 60.5 years, compared with 71.1 years for psoriasis and 75.2 years in naevi controls (https://pubmed.ncbi.nlm.nih.gov/30597518/).
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes – active HS produces substantial decreases in health-related quality of life, which is an issue when adalimumab therapy is frequently insufficient to control HS and other treatment options are currently unavailable.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Adalimumab and other anti-tumour necrosis factor (TNF) alpha drugs are contraindicated in those with a personal or family history of demyelinating diseases such as multiple sclerosis, so bimekizumab (and secukinumab) is a potential option in this HS patient group. Bimekizumab should probably be avoided in those with concomitant inflammatory bowel disease (IBD) because there was a signal in a trial for IBD that it could worsen IBD.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed,	No issues here – the subcutaneous delivery route mirrors adalimumab and secukinumab, and the infrastructure in terms of biologic specialist nurses and home delivery services are already in place. There are no additional baseline or monitoring tests required compared with adalimumab and secukinumab.

additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The current NICE stopping rule for adalimumab and secukinumab in HS could be applied, i.e. if there is less than a 25% reduction in the sum of inflammatory nodules and abscesses then bimekizumab should be discontinued.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Patients report that pain is a key part of living with HS. While some of the functional impact of pain is included in QALY calculations, the burden of living with either chronic pain, or unpredictable episodic pain associated with flares, should not be underestimated. Pain scores of 10/10 (worst pain imaginable) are quite often reported in HS.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, the second anti-IL17 for HS and provides a much-needed alternative to adalimumab. The opportunity to switch biologic therapy will ensure that biologics are started at an appropriate time to prevent scarring, rather than being reserved until substantial scarring has developed, reducing the need for surgery which has high impact on patients and the NHS.
16a. Is the technology a 'step-change' in the management of the condition?	Bimekizumab will provide a step-change in HS management, as the second anti-IL17 therapy available for HS and a much needed alternative biologic for the quite high proportion of HS patients exhibiting primary or secondary failure to adalimumab. Patients' expectations now exceed the 50% improvement in inflammatory lesions denoted

	by the HiSCR trial endpoint and only 50% of HS patients reached even this endpoint in the adalimumab PIONEER studies (Kimball *et al.* 2016, https://pubmed.ncbi.nlm.nih.gov/27518661/).
16b. Does the use of the technology address any particular unmet need of the patient population?	Needed for those with multiple sclerosis in whom anti-TNF therapy is contraindicated and for primary or secondary failure of adalimumab.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are higher rates of candidiasis reported with bimekizumab treatment, however, the candidiasis responds to standard oral therapy. Bimekizumab should be avoided in the small group of HS patients with concomitant active IBD because it could worsen the IBD.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the patient population is moderate-to-severe HS and previous failure of adalimumab treatment was permitted. A recent systematic review highlighted emerging therapies for HS, including bimekizumab https://pubmed.ncbi.nlm.nih.gov/35409118/.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The HIdradenitis SuppuraTiva cORe outcomes set International Collaboration (HISTORIC) has defined six core outcome domains to measure in HS trials (Thorlacius *et al.* 2018 https://pubmed.ncbi.nlm.nih.gov/29654696/): • pain • health-related quality of life • physical signs

	• global assessment (patient & physician) • disease progression (flare frequency/time to recurrence) • other symptoms (drainage & fatigue)
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The trials used all the standard outcome measure instruments, so surrogate outcomes were not needed.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. How do data on real-world experience compare with the trial data?	There are currently limited real-world data for bimekizumab in HS. The UK and Ireland H-STRONG Registry coordinated by the BAD is currently being set up to collect real-world data on HS biologic and other therapies.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Probable higher incidence in people of Afro-Caribbean family background. Please bear in mind that peak prevalence (2%) is in females of child-bearing age.
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• The second anti-IL-17 agent for treating hidradenitis suppurativa (HS) • **Error! Bookmark not defined.**There are no new safety signals for bimekizumab treatment of HS compared to other inflammatory conditions • Bimekizumab will allow biologic therapy for people with HS in whom anti-TNF therapy is contraindicated (e.g. concomitant multiple sclerosis) or when there is primary or secondary failure of adalimumab

Thank you for your time.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisal

Patient survey report

ID6134: Bimekizumab for treating moderate to severe hidradenitis suppurativa

In May 2024, NICE posted an online survey seeking the views of people with hidradenitis suppurativa. This was to ensure the committee could consider patient evidence, as there had not been a patient organisation submission or any patient experts identified.

The survey was publicised by The HS Support Network through their channels. In total, 21 people with experience of the condition responded to the survey. Only one of the responders had personal experience of Bimekizumab.

1. Experience of hidradenitis suppurativa

1.1 Symptoms

Each respondent reported multiple symptoms, ranging from 6 symptoms (N=1) to 14 symptoms (N=1). The average number of symptoms respondents had was 10, and 15 different types of symptoms were identified.

All 21 respondents had experienced:

- Discharge/pus from the lumps.
- General pain and discomfort
- Visible scarring.

Most (N=20) respondents experienced:

- Visible lumps and abscesses
- Difficulty moving or sitting due to painful lumps
- Problems sleeping

Most experienced fatigue (N=19), anxiety (N=17), acne or unwanted excess hair (N=14) and depression (N=14).

Respondents also reported infections (N=11) and high temperature/fever (N=8). Other symptoms included joint pain, dizziness and itching.

1.2 Diagnosis

Out of 20 respondents to this question, around a third (N=7) said it took longer than ten years to be diagnosed from having first symptoms.

20% (N=4) said this took 7-9 years.

15% (N=3) said this took 4-6 years

30% (N=6) said this took 1-3 years

No respondents said this took less than a year.

1.3 Impact on daily life

All respondents described the significant impact hidradenitis suppurativa had on their life. This included daily activities (N=21), ability to socialise (N=20), hobbies (N=19), their ability to work (N=18), and family life (N=16).

1.4 Impact on mobility

Of 19 people who responded, 90% (N=17) reported that their condition affected their mobility.

When asked to explain how mobility was affected, respondents said this depended on the severity, size and area of a flare up.

Over half of comments (N=10) said that if this was on the limbs, groin or armpits then overall mobility was affected.

Around a third of comments (N=6) described how pain limited movement, and made walking, lifting, bending and sitting difficult.

10% of comments (N=2) noted how dressings inhibit movement, which can be at awkward angles.

> 'Flares on the groin or thigh make it very difficult to walk or even sit on the toilet. Flares under the arms or breasts make it difficult to lift anything, cook or clean. All flares make it difficult to sleep.'

1.5 Impact on mental health

Of the 21 respondents, 20 reported that living with the condition affected their mental health.

45% (N=9) said they had experienced anxiety.

40% (N=8) described embarrassment or self-consciousness about their body and 20% (N=4) said they were affected by social anxiety and isolation.

40% (N=8) said they had experienced depression, with two people stating that they'd had suicidal thoughts.

35% (N=7) said they felt stress, anger and frustration.

Other impacts include: low mood (N=2), inability to sleep (N=1), inability to focus (N=1), paranoia (N=1) and trauma/PTSD (N=1).

Respondents also described contributing factors:

- Pain and discomfort (N=4)
- Need to continue working/fulfil commitments (N=3)
- The condition affects all aspects of life (N=2)
- The length of time living with the condition (N=2)

- Limited treatment options (N=2)
- Worry about smell (N=2)
- Worry about dressings (N=1)
- Worry about surgery (N=1)

‘I get frustrated when I have pain or open wounds and it causes constant pain.’

‘I often feel down due to living with this condition for nearly 49 years, with limited treatment. Stress (from) having to try and work full time and manage a relationship. Feeling down and letting other down.’

‘It’s so stressful to go out looking and feeling like a monster with puss bags ready to leak and smell all over the place. It’s degrading and embarrassing. I don’t want to be stared at. I’m not a circus animal but with HS it can make me feel like one. I hate it and I hate my life with HS.’

‘It makes one reclusive, anxious, paranoid, depressed, suicidal and constantly stressed with (the) lack of answers.’

‘It’s a never-ending cycle of torture, I feel disgusting.’

1.6 Impact on physical pain/discomfort

All of the 21 respondents reported that the condition caused them pain or discomfort.

When asked to describe how the condition caused pain/discomfort on a scale of 1-10 (where 1 = low pain and 10 = extreme pain), around a third of respondents (N=6) scored 10.

The remaining respondents all scored 6 or above: (N=1) scored 9, (N=9) scored 8, (N=3) scored 7, (N=1) scored 6.

When asked to explain the type of pain caused by the condition, respondents described:

- Acute pain (N=16). This included irritation, burning, stinging, stabbing pains, nerve pain, swelling and pain from abscesses and/or cysts.
- Chronic pain (N=5) This included constant dull pain, aching and constant tenderness.
- Pain due to movement or activity (N=5)
- Pain due to surgery (N=2)
- Pain due to scarring (N=1)

Respondents also described emotional pain or fear (N=3) and how difficulty sleeping made pain management harder (N=1).

'Excruciating pain.'

'Like someone is pouring acid on my leg. Really warm burning sensation and causes me to be in agony.'

'I don't think I've gone a day where I've not felt pain below 4. On a bad day, the pain has exceeded 10. It's been unbelievable to the point I'm sobbing.'

'Sharp, lingering, throbbing, stinging when a wound is just open and touching another part of the skin. If the abscess has swollen quite large, pressing the surface can send a deep shooting pain through the body. Mild to moderate swelling makes the area feel constantly tender . . . so you feel fragile and sore . . . or limit movement out of fear of it growing to a stage 3.'

'The deepest wound I have had had to be packed daily by the district nurse for twelve weeks. I was hardly able to move during this time and spent weeks in the house. It took a long time to emotionally recover.'

1.7 Personal care

Of the 21 respondents, 71% (N=15) said they required help with personal care. This included:

- Personal hygiene - toileting, washing and dressing (N=12)

- Wound care (N=8)
- Maintaining a home - laundry and cleaning (N=4)
- Nutrition (N=3)
- Mobility (N=1)
- Transport (N=1)

> ‘Help getting dressed, cleaning and dressing wounds, helping to cook meals, everyday tasks when I have a flare up.’
>
> ‘ . . . to help reduce the symptoms and when distressed, low or in too much of any state to prep their own food (they) will not have a balanced or regular meal pattern.’
>
> ‘Daily cleaning of wounds and application of dressings, cleaning stained bed sheets and clothing’.

2. Standard of care for hidradenitis suppurativa

2.1 Treatments and support

Of 21 respondents, 19 had received treatment and support and 8 different types were identified. Some respondents (N=3) stated that nothing had worked.

Treatments and support included:

- Antibiotics (N=13)

Respondents considered that side effects and reduced efficacy over time outweighed early benefits.

The advantages of this treatment were described in 5 comments. Respondents reported initial relief and reduced (but continued) flare ups.

The disadvantages of this treatment were described in 16 comments. Respondents reported that antibiotics stopped working due to

resistance, with continued and increased frequency of flares and that they did not support wound healing.

It was also noted that some doctors do not like to prescribe topical antibiotics, and that it can be difficult to access treatments in a timely manner.

The side effects mentioned were thrush, gut problems, vomiting (which affected the ability to take other medicines), issues with liver function and orange urine.

The length of time having to take antibiotics (several months) was considered a disadvantage, as was being unable to go out in the sun or drink alcohol. One respondent described feeling lonely as unable to go out with family and friends.

> 'I have had long term doses of different antibiotics so now when I actually need them it's hard to find one that my body isn't used to'

- Biological treatments (N=4)

The advantages of this type of treatment were described in 4 comments.

These respondents reported initial benefits, a good response and no side effects.

The disadvantages of this type of treatment were described in 3 comments. These referred to a lack of effectiveness over time, continued flares and serious side effects.

> 'Adumilab seems to help reduce flares but not stop them.'

- Surgery (N=3)

The advantages of undergoing surgery were described in 3 comments. A key benefit for being that it is the only thing that has worked for some (a

permanent solution in one area for one person). A respondent also explained that although surgery is painful, this is much less than the intense pain of an abscess.

Disadvantages were described in 3 comments. These included the length of time to heal afterwards, the risk of infection and having to take antibiotics for a long time after surgery. The likelihood of flare ups returning in the same place was also mentioned.

> 'The only thing that seems to work is surgery and even that takes 5/6 weeks to heal afterwards and makes me open to infections.'

- Steroids (N=2)

The advantages of steroid cream were described in 3 comments.

Respondents said it seems to help most when flares are active, it helps to dull pain and helps to drain sores faster.

No disadvantages were reported.

- Antimicrobial wash (N=2)

No advantages were reported. One respondent said that this didn't work and that new flares started while using.

- Pain relief (N=2)

One respondent said this was helpful when waiting for other treatments or recovering from surgery. It was noted that side effects (such as drowsiness) can be a disadvantage, as this may affect ability to work.

- Topical treatment not specified (N=2)

No advantages were reported. One respondent said that topical treatments were ineffective.

- Diuretics (N=1)

No advantages or disadvantages given.

2.2 Symptoms not addressed by the current treatments

Of 21 respondents, 19 reported symptoms that were not addressed by their current treatments.

All 19 of these respondents reported multiple symptoms, ranging from 2 (N=1) to 13 unaddressed symptoms (N=2). The average number of unaddressed symptoms respondents had was 9 and 14 different types of symptoms were identified. Most experienced the following unaddressed symptoms:

- General pain and discomfort (N=18)
- Visible scarring (N=18)
- Difficulty moving or sitting due to painful lumps (N=17)
- Problems sleeping (N=16)
- Visible lumps and abscesses (N=16)
- Discharge/pus from the lumps (N=14)
- Anxiety (N=14)
- Acne or unwanted excess hair (N=12)
- Depression (N=12).

Respondents also reported infections (N=8), high temperature/fever (N=6) and other mental health problems (N=1), symptoms from injections (N=1).

3. Bimekizumab for hidradenitis suppurativa

Only one person who completed the survey had been treated with Bimekizumab. Of the 21 respondents, 20 had heard of Bimekizumab, of which 17 would consider taking it if it was offered to them. The 3 respondents who would not consider taking said this was due to concerns about side effects and insufficient evidence.

The 17 people who would consider taking it gave the following reasons:

- They would try anything (N=12)
- A choice of therapy options is needed, due to the limitations of existing treatments (N=5)
- Biological treatments are proven to be effective (N=3)

'I will try anything to be freed from this awful disease. It's taken over my life for nearly 40 years. It impacts my life daily. I want to feel some sort of normality.'

'A choice of therapy options is important to people living with a chronic disease. . . HS has a very significant impact on mental health and social functioning, another treatment option is needed urgently.'

'I already take secunimumab (cosentyx) injections for Ankylosing spondylitis and have found them very helpful with my condition.'

'I'd need to see a lot of research and thorough explanations of why this would be recommended over the existing ones, and what they'd expect it to do differently from them.'

3.1 Perceived benefits and drawbacks of Bimekizumab

No responses were provided to questions in this section and no side effects were reported, as answers to previous questions indicate that only one respondent has been treated with Bimekizumab.

3.2 Patients who might benefit more or less from Bimekizumab

Of the 10 respondents to this question, 3 did not think there were any groups who would benefit more or less than others, and 3 said they didn't know, or would need more information to respond.

Of the remaining 4 respondents, 2 said that everyone had the potential to benefit and should be given the option to try this treatment if it would improve quality of life. Other respondents commented that this would be of benefit to people who have:

- stage 3 or 4 of the condition (N=1)
- not found any other treatments to be effective (N=1)
- other conditions which may restrict treatment and support options (N=2)

3.3 Recommending Bimekizumab to others

Of the 9 respondents to this question, 4 people said they would recommend Bimekizumab to others. One of these respondents said this was because patients should have a choice of treatment.

Of the 4 people who said they did not have enough information, 2 said they would recommend it if there was evidence that it was effective.

One person said they would not recommend it as this may increase the risk of infection and sensitivity.

'I'd recommend the option being made available to people so that patients have a choice.'

'Anything that increases risk of infections and re-occurring ones doesn't make any sense. The aim is to help patients lead an independent life, not put them on something that will make them even more sensitive to the environment they're in.'

'Don't know enough about it yet, but if it works I'd definitely be recommending it.'

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bimekizumab for treating moderate to severe hidradenitis suppurativa ID6134

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with **moderate to severe hidradenitis suppurativa** or caring for a patient with **moderate to severe hidradenitis suppurativa**. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Patient expert statement

Bimekizumab for treating moderate to severe hidradenitis suppurativa ID6134

Part 1: Living with this condition or caring for a patient with moderate to severe hidradenitis suppurativa

Table 1 About you, with moderate to severe hidradenitis suppurativa, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with moderate to severe hidradenitis suppurativa? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with moderate to severe hidradenitis suppurativa? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with moderate to severe hidradenitis suppurativa? **If you are a carer (for someone with moderate to severe hidradenitis suppurativa) please share your experience of caring for them**	I have had Hidradenitis suppurativa from the age 7 and was diagnosed age 14. I have inherited the condition from both sides of my family. I experience severe symptoms which have got worse with age, and have needed multiple wide excision surgeries from my groin and armpits. I have tried all recommended treatments including steroids, adalimumab and antibiotics, including daily IV antibiotics for 6 weeks (twice), but all have had short term effects, with symptoms returning. The condition has had a significant impact on my quality of life, with many restrictions. I have a limited choice of clothing. I had to give up sports and hobbies. I experienced a negative cycle where lack of exercise led to weight gain, I became obese which made symptoms worse, and had to have weight loss surgery, but even after losing weight I still have the same symptoms. I had to give up work as a hairdresser as I was unable to stand for long periods or lift my arms. The condition has had a negative impact on family relationships. I didn't have personal relationships until my late 20s, and this also led to difficulty in deciding whether to have children.

	It has had a negative impact on my mental health, with embarrassment from symptoms, and the mental exhaustion of going through drastic treatments including surgery, only for symptoms to return. When symptoms are severe, I need family members to help me with washing, dressing and with mobility. There is also the additional cost of expensive medical dressings.
7a. What do you think of the current treatments and care available for moderate to severe hidradenitis suppurativa on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I experience severe symptoms which have got worse with age, and have needed multiple wide excision surgeries from my groin and armpits. I have tried all recommended treatments including steroids, adalimumab and antibiotics, including daily IV antibiotics for 6 weeks (twice), but all have had short term effects, with symptoms returning.
8. If there are disadvantages for patients of current NHS treatments for moderate to severe hidradenitis suppurativa (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I have tried all recommended treatments including steroids, adalimumab and antibiotics, including daily IV antibiotics for 6 weeks (twice), but all have had short term effects, with symptoms returning.
9a. If there are advantages of bimekizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does bimekizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of bimekizumab over current treatments on the NHS please describe these. For example, are there any risks with bimekizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from bimekizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering moderate to severe hidradenitis suppurativa and bimekizumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
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Single Technology Appraisal

Bimekizumab for treating moderate to severe hidradenitis suppurativa ID6134

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

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Patient expert statement

Bimekizumab for treating moderate to severe hidradenitis suppurativa ID6134

Part 1: Living with this condition or caring for a patient with moderate to severe hidradenitis suppurativa

Table 1 About you, with moderate to severe hidradenitis suppurativa, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with moderate to severe hidradenitis suppurativa? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with moderate to severe hidradenitis suppurativa? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with moderate to severe hidradenitis suppurativa? **If you are a carer (for someone with moderate to severe hidradenitis suppurativa) please share your experience of caring for them**	I have Hidradenitis suppurativa which presented from the age 11 at the onset of puberty and consistently became worse and worse up until I had severe degradation of my skin. My father and my sister both have HS albeit stage 1 and I have happened to flit between 2-3 for the past 15 years at least. I have tried all recommended treatments except biologics for personal reasons given side effects and no confirmation on fertility as I am of childbearing age. It's not something I would discount and has been discussed before. I manage my disease mainly through surgical treatments which I am about to embark on my 26th operation. I have had a complete graft on both arms at the same time at 19 and continued to manage with taking out heavily diseased areas since. HS has been a huge dark mark over my life and continues to be now, It robbed me of a decent teenage life as I was constantly hiding my arms away, left me with a lot of shame due to ineffective dermotologists who did not understand the disease, self esteem issues, missed career opportunities, relationship issues, horrific flares over pregnancy which led me to not breastfeed due to pain and inflammation on my breasts. There have been times I have sobbed just trying to hold my child and it has put a strain on my relationship due to the physical and mental demands.

	I am fortunate I work in the corporate world but HS limits my career opportunities, I'm can work from home when needed and for the majority of the week but I have been turned down for opportunities given my limitation to travel. I suffer with horrific anxiety which at one point made me agriphobic due to constant catastrophising since my health never seems to improve, this was related to why I have 3 large abscess removed from my face in the space of 6 months. I currently have a blue badge and whilst I like to think I am strong and capable, I do have to utilise my support network as much as possible, even for things like washing my hair, helping me put a bra on. It's no life to be having at 34. I have also felt shamed and blamed at points in my medical journey, HS is debilitating, it is painful to breathe sometimes let alone exercise regularly, weight loss being banded around has made me feel like I am the issue at times because I physically can't move, without delving into the psychological impacts and seeking comfort in "unhealthy" habits.
7a. What do you think of the current treatments and care available for moderate to severe hidradenitis suppurativa on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I believe they are somewhat limited, they are rooted in trial and error and similar disease progress and taking Roaccutane for HS for example, should not be a patient pathway. This is not an uncommon disease and we deserve licenced medicine that has a direct effect on HS. I know there are similar thoughts, coupled with the fact that not everyone has the privledge to attend a HS specific clinic, that people are still being held up at GP Surgeries taking tetracyclines and being subtly told they are the issues with weight etc.

8. If there are disadvantages for patients of current NHS treatments for moderate to severe hidradenitis suppurativa (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Side effects are not ones that can be lived with easily with a lot of biologics, we aren't talking heart burn here, we are talking severe life alterting side effects at times. The economic impact too of having to potentially take time out of work, attend check ups, dedicate whats essentially a part time job hours into managing your dosages.
9a. If there are advantages of bimekizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does bimekizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
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11. Are there any groups of patients who might benefit more from bimekizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	

dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering moderate to severe hidradenitis suppurativa and bimekizumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bimekizumab for treating moderate to severe hidradenitis suppurativa [ID6134]

Clinical expert statement

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NICE National Institute for Health and Care Excellence

Part 1: Treating moderate to severe hidradenitis suppurativa and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Emma McMullen
2. Name of organisation	[redacted]
3. Job title or position	Consultant Dermatologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with moderate to severe hidradenitis suppurativa? ☐ A specialist in the clinical evidence base for moderate to severe hidradenitis suppurativa or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a

8. What is the main aim of treatment for moderate to severe hidradenitis suppurativa? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve quality of life, reduce pain, reduce odour, reduce draining, reduce/prevent irreversible scarring
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Patients able to work without pain, not take sick days, improvement in HiSQoL of 10 points, DLQI of 4 points, reduction in lesion count by 30% or more
10. In your view, is there an unmet need for patients and healthcare professionals in moderate to severe hidradenitis suppurativa?	Yes, we only have 2 licensed treatments and one is ineffective in some patients and response wanes with time, the other is contraindicated in certain patient groups and can be ineffective/not achieve treatment goals
11. How is moderate to severe hidradenitis suppurativa currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	BAD clinical guidelines Treated with oral antibiotics, surgery, pain management, biologics, antiandrogens in women, or a combination of these. Most treatments are suboptimal or stop working so patients are frequently left in pain, often admitted to hospital for flares The medication bimekizumab appears from the data to be more effective than current available treatments
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	It should be used in the same way as current biologic therapies, but should be more effective This should be used in a secondary care dermatology setting Most secondary derm services already have the infrastructure to prescribe and monitor this treatment

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I expect this tech to significantly increase quality of life in these patients, reduce the need for surgery and reduce the need for frequent hospital admissions and outpatients visits
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	??
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	no
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No active inflammatory bowel disease, active infection, pregnancy – relative contraindications
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The disease is quite different from some other inflammatory skin disease so it is better to use a disease specific QoL measurement such as the Hi SQoL and also to look a work related absence
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes – first IL 17 A and F inhibitor Gives higher efficacy and improved quality of life compared to other drugs
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Increased risk of infection – this is manageable and similar for existing biologic therapies
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes HiSCR, DLQI, all patient related outcome measures including pain score and work related outcomes Re adverse effects – this drug has been used in psoriasis for some time and I am not aware of any unforeseen adverse effects
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 935 [TA935]?	No
23. How do data on real-world experience compare with the trial data?	Not aware
24. In NHS practice, for people who have previously received adalimumab but are currently receiving bimekizumab or secukinumab: **- What treatment(s) would primary non-responders receive (following assessment of response at 16 weeks)?** **- What treatment(s) would people receive following partial loss of response (some treatment response below the HiSCR25 threshold) beyond the first 16 weeks of treatment (i.e. secondary non-responders)?**	We have no other better medical treatment options beyond adalimumab or secukinumab currently They may be admitted for extensive surgery or iv Ertapenum if very severe Otherwise we are looking to other non-licensed ineffective treamtents
25. In NHS practice, would adalimumab be restarted as a third-line treatment following previous treatment with adalimumab and secukinumab/bimekizumab?	Occasionally, but is unlikely to be of benefit
26. For people treated with best supportive care, would people be expected to experience improvements in symptoms or only decline/worsening in symptoms?	Normally decline/worsening
26. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	This tend to affect more females 3:1 This tend to be more severe in those of Arfrican or Asian ethnicity It affects women of childbearing age – there is a higher rate of congenital abnormalities and Caesarean section in those with HS

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

We have only 2 licensed treatment which can be ineffective/suboptimal for many patients

This is a painful, embarrassing, life-limiting, chronic, scarring disease which currently has treatments which only offer a 40% improvement in symptoms

The mental health impact of HS in patients is huge – suicide risk (OR 2.08), depression (1.84)

Response rates significantly higher than that of previous approved treatments 75% patients achieving HiSCR50, 55% HiSCR75 at week 48 (16 weeks data : 42-45% with secukinumab, 41.8%- 58% adalimumab)

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Part 1: Treating moderate to severe hidradenitis suppurativa and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr John Ingram
2. Name of organisation	British Association of Dermatologists (BAD)
3. Job title or position	Clinical Reader & Consultant Dermatologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with moderate to severe hidradenitis suppurativa? ☒ A specialist in the clinical evidence base for moderate to severe hidradenitis suppurativa or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes – please see my answers to the additional questions on page 7
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

8. What is the main aim of treatment for moderate to severe hidradenitis suppurativa? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in moderate to severe hidradenitis suppurativa?	
11. How is moderate to severe hidradenitis suppurativa currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 935 [TA935]?	
23. How do data on real-world experience compare with the trial data?	
24. In NHS practice, for people who have previously received adalimumab but are currently receiving bimekizumab or secukinumab: **- What treatment(s) would primary non-responders receive (following assessment of response at 16 weeks)?** **- What treatment(s) would people receive following partial loss of response (some treatment response below the HiSCR25 threshold) beyond the first 16 weeks of treatment (i.e. secondary non-responders)?**	Primary non-responders would be switched to another therapy, options including oral therapy such as antibiotics, surgery, or possibly resumption of adalimumab therapy if this was previously preventing disease progression. For secondary non-responders, co-therapy to re-establish sufficient response might be considered. For example, antibiotics, metformin, or surgery. There is also the option to submit an individual funding request for a non-approved biologic/ novel small molecule therapy, however this would be in a relatively small number of patients with rapidly progressing disease.
25. In NHS practice, would adalimumab be restarted as a third-line treatment following previous treatment with adalimumab and secukinumab/bimekizumab?	This is possible – in some cases benefit from previous treatment becomes more apparent when treatment is stopped. This can unmask disease progression that was previously prevented on treatment.
26. For people treated with best supportive care, would people be expected to experience improvements in symptoms or only decline/worsening in symptoms?	HS undergoes relapses and remissions, however disease progression in the long term is likely with only best supportive care.
26. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

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External Assessment Group Report
Bimekizumab for treating moderate to severe hidradenitis suppurativa [ID6134]

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Joseph Lord performed the critical review of the economic analyses, validated the economic model, and drafted Sections 4, 5, and 6 of the report.

Mark Perry and Ros Wade performed the critical review of the clinical effectiveness evidence and wrote Sections 2 and 3 of the report.

Melissa Harden reviewed the company's search strategies and contributed to Sections 3 and 4 of the report.

Matthew Walton oversaw the critical review of the economic analyses, the EAG additional analyses, validation of the economic model, drafted Sections 4, 5 and 6 of the report, and takes responsibility for the economic sections of the report.

Mark Simmonds provided advice, wrote some parts of Section 3 of the report, and takes overall responsibility for the report.

Note on the text
All commercial-in-confidence (CIC) data have been highlighted in blue and underlined.

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List of abbreviations

A&E	Accident and emergency department
ABX	Antibiotics
ADA	Adalimumab
AE	Adverse event
ALT	Alanine aminotransferase
AMS	Active medication set
AN	Abscess and inflammatory nodule
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BAD	British Association of Dermatologists
BKZ	Bimekizumab
BMI	Body mass index
BSC	Best supportive care
CHE	Centre for Health Economics
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CQ	Clarification question
DIC	Deviance information criteria
DLQI	Dermatology Life Quality Index
DT	Draining tunnel
EAG	External Assessment Group
EAIR	Exposure-adjusted incidence rates
EMA	European Medicines Agency
EQ-5D-3L	5-dimension, 3-level EuroQol questionnaire
FDG	Final draft guidance
GLM	Generalised logit model
HiSCR	Hidradenitis Suppurativa Clinical Response
HiSCR25	25% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining tunnel count
HiSCR50	50% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining tunnel count
HiSCR75	75% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining tunnel count
HiSCR90	90% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining tunnel count
HiSCR100	100% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining tunnel count
HiSCR-er	Hidradenitis Suppurativa Clinical Response excluding the surgical site
HiSQOL	Hidradenitis Suppurativa Quality of Life
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HS	Hidradenitis suppurativa
HSSA	Hidradenitis Suppurativa Symptoms Assessment
HSSDD	Hidradenitis Suppurativa Symptom Daily Diary
HSSQ	Hidradenitis Suppurativa Symptom Questionnaire
HTA	Health technology assessment
IBD	Inflammatory bowel disease
ICE	Intercurrent event

ICER	Incremental cost-effectiveness ratio
IgG1	Immunoglobulin G1
IHS4	International Hidradenitis Suppurativa Severity Score System
IHS4-55	55% reduction in IHS4 total score
IL	Interleukin
MAIC	Matching-adjusted indirect comparison
MCMC	Markov Chain Monte Carlo
MI	Multiple imputation
mNRI	Modified non-responder imputation
NHB	Net health benefit
NMA	Network meta-analysis
NRS	Numerical rating scale
OC	Observed cases
OHE	Office of Health Economics
OLE	Open-label extension
OR	Odds ratio
PAS	Patient access scheme
PCDS	Primary Care Dermatology Society
PBO	Placebo
QALY	Quality-adjusted life year
QW	Every week
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RCT	Randomised controlled trial
RR	Risk ratio
RS	Randomised set
SAE	Serious adverse event
SD	Standard deviation
SEC	Secukinumab
SF-12	12-item short form health survey
SF-36	36-item short form health survey
SIB	Suicidal ideation and behaviour
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SS	Safety set
STA	Single Technology Appraisal
TEAE	Treatment-emergent adverse event

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence, and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

Table 1 Overview of EAG's key issues

1.1 Overview of the EAG's key issues

ID	Summary of issue	Report sections
1	Limited evidence on the relevant population of people with prior exposure to adalimumab	3.3.3, 3.4, 3.7, 4.2.3, 4.2.6, 6
2	Limited evidence on outcomes for patients receiving the recommended dosing schedule for bimekizumab	3.4, 3.7
3	Lack of direct evidence comparing bimekizumab to secukinumab	3.8, 3.9, 3.10
4	Third-line use of adalimumab following discontinuation of bimekizumab and secukinumab is unlikely to represent NHS practice	4.2.4, 4.2.8.1, 6
5	Up-titration of secukinumab inappropriately modelled and may underrepresent effectiveness of secukinumab in NHS	4.2.4
6	Incorrect implementation of stopping rule for secondary non-responders underestimates costs and QALYs on active treatment	4.2.2, 4.2.4, 4.2.6.2, 4.2.8.1, 6
7	Durable response assumption on BSC awards permanent treatment effect to patients discontinuing active therapies	4.2.2, 4.2.6.1, 6
8	Constraints imposed on BSC maintenance phase transitions underestimates BSC outcomes	4.2.6.1, 6
9	Application of placebo response outcomes to patients who discontinue active treatment	4.2.6.1, 6
10	Selective imposition of disease-related mortality may be inappropriate	4.2.6.3, 6
11	Analysis and implementation of health state utilities	4.2.7, 6

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The EAG prefers the use of the NMA to derive BSC transition probabilities;
- The EAG prefers to remove the 'durable response' assumption for BSC transition probabilities beyond Week 48;

- The EAG prefers stopping rules to be consistent with those established in previous appraisals;
- The EAG prefers the use of maintenance phase transition probabilities for BSC when used as a subsequent therapy, rather than placebo response rates;
- The EAG prefers to use surgery-related hospitalisation costs aligned with previous appraisals.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients achieving a HiSCR response;
- Increasing the proportion of patients achieving higher levels of HiSCR response;
- Allowing more patients to benefit from assumptions applied to the effectiveness of BSC, prolonging the time over which patients maintain a response to treatment.

Overall, the technology is modelled to affect costs by:

- Higher treatment acquisition costs;
- Reducing resource use associated with management of HS;
- Patients remaining on active treatment for longer.

The modelling assumptions that have the greatest effect on the ICER are:

- Assumptions around how BSC effectiveness is modelled, especially when used as a subsequent therapy after discontinuation;
- Application of stopping rules for bimekizumab and secukinumab.

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission was restricted to optimise the cost effectiveness of bimekizumab. The population was restricted to people for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment. The EAG agrees with this modification and has consequently focused its report on the 'biologic-experienced' subpopulation as being closest to the proposed population. Limitations of the evidence for the 'biologic-experienced' subgroup are discussed below.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Limited evidence on people with prior exposure to adalimumab

Report section	3.3.3, 3.4, 3.7 4.2.3, 4.2.6, 6
Description of issue and why the EAG has identified it as important	The target population is people with prior exposure to adalimumab, or people for whom adalimumab is unsuitable. Much of the trial evidence on bimekizumab, however, was in patients who had not received adalimumab. Restricting analysis to "biologic-experienced" patients substantially reduced the size of the population considered, and so increased uncertainty in all effect estimates. In addition, some biologic-experienced patients received treatments other than adalimumab, and this population does not necessarily include patients for who adalimumab was unsuitable. Therefore, the evidence presented does not precisely match the target population. There may be differences in outcomes on bimekizumab between biologic-experienced and biologic-naïve patients. The model may therefore over-estimate the effectiveness of bimekizumab in an NHS setting.
What alternative approach has the EAG suggested?	The EAG considers the use of subgroup analysis based on prior biologic experience potentially informative, but recognises that due to small sample sizes these results may be subject to a high level of uncertainty in the cost-effectiveness results.
What is the expected effect on the cost-effectiveness estimates?	A model capable of running deterministic and probabilistic analysis on the subgroup results has not been provided by the company. Subgroup results using the company base case assumptions was provided but could not be validated by the EAG. The company reported an ICER for bimekizumab in biologic experienced patients of £2,319 versus secukinumab.
What additional evidence or analyses might help to resolve this key issue?	A model capable of running deterministic and probabilistic analysis on the subgroup results must be provided by the company for validation, to allow probabilistic analysis to be undertaken, and to allow application of the EAG's alternative assumptions.

Issue 2 Limited evidence for patients receiving the recommended dosing schedule for bimekizumab

Report section	3.4, 3.7
Description of issue and why the EAG has identified it as important	The BE HEARD trials included three bimekizumab arms with differing dosing regimens: every 2 weeks; every 4 weeks; every 2 weeks for 16 weeks and every 4 weeks thereafter. Only the last of these matches the recommended dosing schedule. The 16-week (placebo controlled) data for the two groups that received bimekizumab every 2 weeks for the first 16 weeks is relevant to the decision problem/recommended dosing schedule (n=580). However, only the treatment arm receiving the recommended dosing schedule provides relevant 48-week data (n=292).
What alternative approach has the EAG suggested?	The EAG has preferred to focus on the recommended dosing schedule where possible, noting any differences with other doses.
What is the expected effect on the cost-effectiveness estimates?	Limited evidence for patients receiving the recommended dosing schedule of bimekizumab may introduce additional uncertainty into the cost-effectiveness results.
What additional evidence or analyses might help to resolve this key issue?	Further outcome data for patients receiving the recommended bimekizumab dosing schedule is required.

Issue 3 Lack of direct evidence comparing bimekizumab to secukinumab

Report section	3.8, 3.9, 3.10
Description of issue and why the EAG has identified it as important	No head-to-head trials of bimekizumab and secukinumab exist: only indirect evidence is available. The BE HEARD trials of bimekizumab were pooled together, as were the SUNSHINE/SUNRISE trials of secukinumab. Consequently, although NMAs and MAICs were performed, these analyses are effectively comparisons of just two trials, with potential for bias if the trials have different characteristics. There were some differences in several potential outcome modifiers (weight, BMI, Hurley stage, DLQI, IHS4 and antibiotic use) across comparisons, making inconsistency possible. However, since there were no loops in the network it was not possible to formally evaluate inconsistency. The EAG therefore considers that the results of indirect comparisons of bimekizumab and secukinumab should be treated with caution.
What alternative approach has the EAG suggested?	None is feasible at present.
What is the expected effect on the cost-effectiveness estimates?	The lack of direct evidence on the relative effectiveness of bimekizumab and secukinumab results in uncertainty in the relative cost-effectiveness of each treatment option.
What additional evidence or analyses might help to resolve this key issue?	Well conducted head-to-head trials comparing bimekizumab and secukinumab in the population of interest would be needed to confirm the relative effectiveness of the treatments.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 4 Third-line use of adalimumab following discontinuation of bimekizumab and secukinumab is unlikely to represent NHS practice

Report section	4.2.4, 4.2.8.1, 6
Description of issue and why the EAG has identified it as important	The company assume that 20.8% of patients who discontinue bimekizumab and secukinumab would be switched to adalimumab. This use of adalimumab is not recommended by NICE and to the EAG's knowledge is not funded on the NHS. Acquisition of adalimumab comprises around 40 - 41% of total costs in the bimekizumab and secukinumab arms of the model. Clinical advice to the company and EAG suggests it is plausible that a proportion of patients may instead continue to receive their current biological therapy following a partial loss of response.
What alternative approach has the EAG suggested?	The EAG presents a scenario in which 20.8% of patients on the active treatment arms continue to receive bimekizumab or secukinumab as appropriate alongside BSC following a loss of response. This analysis assumes that this proportion represents those who are still exhibiting some treatment response below the HiSCR25 threshold.
What is the expected effect on the cost-effectiveness estimates?	This scenario reduces total costs on bimekizumab and secukinumab relative to BSC. [redacted] the pairwise ICER versus secukinumab is reduced to £79 in the EAG-corrected company base case, and to £8,644 compared to BSC.
What additional evidence or analyses might help to resolve this key issue?	Clarity on whether primary non-responders would also continue treatment at a similar frequency to those partially losing response beyond Week 16 is needed. Clarity from NHS England on whether adalimumab can be re-started at third line would be informative in determining which of the company or EAG preferences are most relevant. Information on current prescribing practices in the NHS would be informative in resolving this issue.

Issue 5 Up-titration of secukinumab inappropriately modelled and may underrepresent effectiveness of secukinumab in NHS

Report section	4.2.4
Description of issue and why the EAG has identified it as important	The marketing authorisation for secukinumab allows for the standard Q4W maintenance dose to be increased to Q2W in patients who do not achieve a response at Week 16, or who have a body weight of 90 kg or higher. This may induce response in more patients on secukinumab, and is likely to reflect NHS practice, although there is limited evidence on the effectiveness of this strategy. The company provided model results including an approximation of up-titration for secukinumab in their clarification response. This was based on 36 weeks of additional treatment rather than 12. It was unclear to which group of non-responders the 'relaxation of stopping rules' was applied. The company did not provide this functionality in the model in time for the EAG to validate .
What alternative approach has the EAG suggested?	Scenarios including up-titration should be implemented in accordance with the secukinumab licence, and considered in addition to secukinumab without up-titration. That is, non-responders at Week 16 should be modelled to up-titrate to Q2W for a further 12 weeks, with the ability to achieve a response during this period. Those who remain non-responders after this point should discontinue treatment.
What is the expected effect on the cost-effectiveness estimates?	If appropriately implemented in the model, the inclusion of up-titration of secukinumab would increase total QALYs relative to bimekizumab due to a larger proportion of patients achieving a response. Whilst Q2W secukinumab is available at the same price as Q4W, total costs on secukinumab would be higher, as patients would remain on treatment for longer. The net effect upon its cost-effectiveness relative to bimekizumab is uncertain.
What additional evidence or analyses might help to resolve this key issue?	Up-titration of secukinumab should be implemented in the economic model in line with the marketing authorisation and the description of this scenario in TA935.

Issue 6 Incorrect implementation of stopping rule for secondary non-responders underestimates costs and QALYs on active treatment

Report section	4.2.2, 4.2.4, 4.2.6.2, 4.2.8.1, 6
Description of issue and why the EAG has identified it as important	The company assumed that patients on bimekizumab and secukinumab who lost response during maintenance treatment discontinued treatment immediately. The committee accepted in TA935 that treatment should only be discontinued when a patient stops responding, and maintains non-response for 12 weeks, typically following additional treatment and/or surgery to re-establish response. Around [redacted]% of non-responders should regain response to bimekizumab in a given maintenance phase cycle based on BE HEARD. This means that while [redacted] of Week 16 responders to bimekizumab in BE HEARD discontinued by Week 48, the model predicts discontinuation of [redacted] in this same period. The model therefore fails to capture a significant component of the treatment effect (i.e. the ability to regain and maintain a treatment response), and the costs associated with continuation of treatment. The model is in this way unable to determine the relative effectiveness of alternative treatment options.
What alternative approach has the EAG suggested?	The model structure should be amended for consistency with that accepted in TA935. The stopping rule should be modelled using a series of tunnel states. Only when a patient has maintained non-response for 3 consecutive cycles should they discontinue. The EAG has implemented an approximation of this stopping rule in an alternative base case, assuming a smaller proportion of patients in the non-response health state discontinue in a given cycle.
What is the expected effect on the cost-effectiveness estimates?	Total costs predicted by the model for bimekizumab and secukinumab are likely to increase substantially relative to BSC. The number of additional QALYs generated by the full implementation of this stopping rule is unclear. The EAG scenario described above increases total QALYs by [redacted] and [redacted] for secukinumab and bimekizumab respectively. Pairwise ICERs for bimekizumab versus secukinumab and BSC respectively are increased to £25,602 and £17,677 when the scenario is applied to the EAG-corrected company base case.
What additional evidence or analyses might help to resolve this key issue?	The stopping rule for secondary non-responders as accepted in TA935 should be implemented in the executable model.

Issue 7 Durable response assumption on BSC awards permanent treatment effect to patients discontinuing active therapies

Report section	4.2.2, 4.2.6.1, 6
Description of issue and why the EAG has identified it as important	Patients on BSC remain in their current health state indefinitely beyond Week 48 of the model. Patients discontinuing active treatment can in this way retain the level of response they have achieved indefinitely. Furthermore, those who discontinue due to non-response can achieve response to BSC based on initial period placebo outcomes, and maintain outcomes indefinitely upon reaching Week 48 of the model. The primary benefit of active treatment in the model arises through the manipulation of BSC outcomes. The application of a permanent treatment benefit for patients who discontinue active therapy is inappropriate and benefits treatments with higher rates of secondary non-response. This assumption results in response rates of [redacted] in perpetuity on bimekizumab, compared to [redacted] on BSC, despite >99% of patients having discontinued treatment. This assumption alone generates ~75% of incremental QALYs attributed to bimekizumab compared to secukinumab and BSC in the company's base case.
What alternative approach has the EAG suggested?	In the submitted model, the value case for bimekizumab is built around an incentive to discontinue active treatment closest to Week 48 and thus for a larger proportion of patients to receive permanent BSC placebo response outcomes. The EAG prefers a model structure which allow patients to transition freely between health states indefinitely on BSC, and thus treatment efficacy is less dependent upon BSC assumptions. The EAG is not in principle opposed to a response rate plateau on BSC, but this must be implemented using a tunnel state structure which allows patients who discontinue active treatment to experience 48 weeks of BSC outcomes to prevent clinically implausible long-term response rates.
What is the expected effect on the cost-effectiveness estimates?	Removing the assumption of durable response to BSC increases pairwise ICERs for bimekizumab to £42,216 and £86,759 in the EAG-corrected company base-case analysis. This scenario should be considered alongside more clinically plausible estimates for BSC outcomes as in Issue 8.
What additional evidence or analyses might help to resolve this key issue?	Input on the clinical plausibility of a response plateau resulting in more patients previously treated with active therapy achieving life-long benefits. Structural changes should be made to the model allowing discontinuing patients to experience BSC outcomes for at least 48 weeks before applying a plateau.

Issue 8 Constraints imposed on BSC maintenance phase transitions underestimates BSC outcomes

Report section	4.2.6.1, 6
Description of issue and why the EAG has identified it as important	Transitions for patients on BSC were restricted to continuation in their current health state or decline during the maintenance treatment period. This is an incomplete representation of the natural history of HS, which is a condition characterised by transient exacerbations and improvements induced by treatment and surgery. The model significantly underestimates the proportion of responders to BSC at any given time. Transitions to higher levels of response were not possible for any patients on BSC beyond Week 16. This resulted in a proportion of patients with a >HiSCR50 response at Week 36 of [redacted] in the model, compared to 15.9% in PIONEER II (which likely underrepresents response to NHS BSC), and [redacted] predicted using the NMA to adjust bimekizumab transition probabilities. This artificially deflates QALY gain on BSC and is inconsistent with previous appraisals.
What alternative approach has the EAG suggested?	The EAG favours the use of the NMA to adjust bimekizumab maintenance phase transition probabilities to derive transitions for BSC after Week 16. This allows patients to lose and regain response over time. Scenarios using a linear fit to the PIONEER II loss of response rate should represent the lower bound of plausible BSC maintenance phase outcomes, representing a scenario in which patients can only lose or maintain response. This assumption interacts strongly with that described in Issue 7, and the scenarios described should be considered in combination.
What is the expected effect on the cost-effectiveness estimates?	Modelling BSC outcomes using loss of response rates derived from PIONEER II and removing the 'durable response' assumption increases ICERs for bimekizumab to £21,818 and £50,543 versus secukinumab and BSC respectively in the EAG-corrected company base case. Using the NMA to adjust BSC outcomes generates equivalent ICERs of £56,647 and £122,804.
What additional evidence or analyses might help to resolve this key issue?	Clinical input on whether outcomes on BSC include improvements in symptoms (NMA) or only decline (PIONEER II).

Issue 9 Application of placebo response outcomes to patients who discontinue active treatment

Report section	4.2.6.1, 6
Description of issue and why the EAG has identified it as important	Patients who discontinued from active treatment due to primary or secondary non-response were subject to short-term placebo response outcomes from the BE HEARD studies for 12 weeks. When combined with the assumption that response is maintained beyond Week 48 on BSC, this generated a significant proportion of the QALY benefit of active treatments. This associated loss of response to active treatment with a substantial boost to response rates, based on trial placebo response. A significant component of placebo response in a trial setting is a patient's belief that they are may be receiving an effective therapy as well as regression to the mean. In an NHS setting, a patient who is unblinded to the fact they have stopped receiving an active treatment may be unlikely to experience to a placebo response beyond the cycles of exacerbation and improvement inherent to HS and its management.
What alternative approach has the EAG suggested?	Presently, the value case for bimekizumab is built around the tunnel state system which applies BSC placebo response outcomes. The closer these transitions are applied to Week 48, the more benefit a treatment receives. The EAG suggest the application of maintenance phase BSC outcomes from the point of discontinuation may better represent the outcomes of patients who discontinue active therapy.
What is the expected effect on the cost-effectiveness estimates?	When BSC maintenance phase transition probabilities are applied to patients discontinuing active treatment immediately, incremental QALYs for bimekizumab drop to [redacted] and [redacted] versus secukinumab and BSC respectively, producing respective ICERs of £67,897 and £249,940. When BSC NMA outcomes are applied instead of the company's 'gradual deterioration' assumption (per Issue 8), ICERs for bimekizumab are £57,028 and £137,408 versus secukinumab and BSC respectively.
What additional evidence or analyses might help to resolve this key issue?	Clinical advice on whether patients discontinuing active therapy would be expected to experience a placebo response-like boost to response rates, or natural history-like outcomes.

Issue 10 Selective imposition of disease-related mortality may be inappropriate

Report section	4.2.6.3, 6
Description of issue and why the EAG has identified it as important	A standardised mortality ratio (SMR) of 1.86, reflecting excess mortality in patients who have undergone surgery for severe HS, was applied only to patients in the non-response health state. The source study also reports an adjusted SMR of 1.48. All patients who achieved a response were subject to general population mortality risks. The EAG understands that excess mortality related to HS is attributable to both acute sources (i.e. surgery) and long-standing metabolic and cardiovascular co-morbidities, which are not fully resolved immediately upon achieving a response to treatment. It is unclear whether it is appropriate that patients in the response health states are exempt from this excess mortality risk.
What alternative approach has the EAG suggested?	The EAG prefers to explore the impact of scenarios which include excess mortality to patients who respond to treatment, and the use of an SMR adjusted for patient characteristics.
What is the expected effect on the cost-effectiveness estimates?	In the EAG-corrected company base case, applying general population mortality rates to all health states results in dominance for bimekizumab over secukinumab, and an ICER of £12,176 versus BSC. When applying an SMR of 1.86 to all health states, bimekizumab remains dominant versus secukinumab, and has an ICER of £14,127 versus BSC. Applying an SMR of 1.48 to all patients results in an ICER of £691 versus secukinumab, and £13,287 versus BSC.
What additional evidence or analyses might help to resolve this key issue?	Evidence on mortality rates in HS patients successfully treated with adalimumab would help resolve this issue. Input on the relationship between duration of response and reduction in the burden of co-morbidities in HS may inform a more sophisticated and realistic implementation of mortality.

Issue 11 Analysis and implementation of health state utilities

Report section	4.2.7, 6
Description of issue and why the EAG has identified it as important	Subdivision of EQ-5D data from BE HEARD by treatment and phase was not based on statistically significant differences between groups and may artificially increase QALYs on active treatment.
What alternative approach has the EAG suggested?	The EAG proposes alternative health state utility value sets based on a re-analysis of the BE HEARD utility data which applies a treatment-specific utility only to non-responders. This better reflects the underlying mechanism of treatment and the statistical significance of the utility analysis. These value sets have been integrated into the analyses presented by the EAG
What is the expected effect on the cost-effectiveness estimates?	Using phase-specific utilities pooled by treatment arm except for the non-response health state in the EAG-corrected company base case, bimekizumab dominates secukinumab, and has an ICER of £10,897 versus BSC. Using a single value set pooled by health state and treatment phase generates ICERs of £2,543 and £14,621 versus secukinumab and BSC respectively.
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion on which is the most plausible value set should be sought by the committee. There is no new evidence required to inform this issue.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Where possible, the EAG has attempted to address or illustrate the impact of the above issues, but the EAG emphasises that it does not consider it possible to fully capture the differential costs and benefits of each treatment option in the model as presented. The issues highlighted by the EAG are largely interconnected, and by removing the assumption of 'durable response' to BSC, the apparent benefits of bimekizumab largely disappear. This is not because bimekizumab is an ineffective treatment, but rather that the primary mechanism of value generation in the model is not based upon achieving a long-term response on bimekizumab. Instead, it is through maximising benefit derived from the 'durable response' assumption, whilst ensuring the comparators receive minimal benefit from BSC. Important structural changes which fully propagate the trial and synthesis results through the model must be made before the model can be considered fit for decision making purposes.

The EAG presents two combinations scenarios in two alternative base cases. This reflects two interpretations of the economic analysis submitted by the company. The first (EAG base case 1) removes the model assumptions the EAG have identified as either clinically implausible, or as artificially and selectively imposing certain treatment benefits for bimekizumab. This scenario essentially represents the benefit of bimekizumab perpetuated through the model from the trial-

derived transition probabilities and HRQoL data alone, rather than assumptions relating to BSC effectiveness. That is, this scenario demonstrates the extent to which the current model structure can capture the benefits of bimekizumab. However, the issue remains that long-term treatment and its outcomes are not captured due the company's approach to modelling discontinuation.

The second EAG base case (EAG base case 2) adopts a clinically plausible alternative set of assumptions which the EAG consider to more fairly represent the differential cost-effectiveness of secukinumab and bimekizumab. Comparisons with BSC are more limited in their utility. The EAG considers this analysis more methodologically consistent both internally and with previous appraisals, and the most clinically plausible of the analyses presented.

However, the EAG again emphasises that it does not consider the model structure as presented to be appropriate for capturing the differential benefits of all treatment options. In particular, absolute costs and QALYs, and those of active treatments relative to BSC, are subject to a high degree of uncertainty. Important structural changes must be made before the model can be considered fit for decision making purposes. The results of the EAG's alternative base-case analyses are presented in Table 1 and Table 2, with probabilistic results in Table 3.

Table 1 Summary of EAG preferred assumptions (EAG base case 1)

Scenario	Bimekizumab vs	Inc. cost	Inc. QALYs	ICER	Change from company base case
Company base case (uncorrected)	Secukinumab	[redacted]	[redacted]	£3,605	-
	BSC	[redacted]	[redacted]	£12,444	-
EAG-corrected company base case	Secukinumab	[redacted]	[redacted]	£2,200	-£1,405
	BSC	[redacted]	[redacted]	£12,437	-£7
Scenario 2: Replace adalimumab in BSC with discontinued active treatment.	Secukinumab	[redacted]	[redacted]	£79	-£3,526
	BSC	[redacted]	[redacted]	£8,644	-£3,800
Scenario 3: 70-year time horizon.	Secukinumab	[redacted]	[redacted]	£2,213	-£1,392
	BSC	[redacted]	[redacted]	£12,434	-£10
Scenario 5: Use transition probabilities based on the NMA to represent the effectiveness of BSC (Week 16+)	Secukinumab	[redacted]	[redacted]	£56,647	£53,042
	BSC	[redacted]	[redacted]	£122,804	£110,360
Scenario 7: Apply 12 weeks of active treatment costs to secondary non-responders following discontinuation.	Secukinumab	[redacted]	[redacted]	£3,190	-£415
	BSC	[redacted]	[redacted]	£16,067	£3,623
Scenario 10: Disease-related mortality for all patients (SMR 1.86).	Secukinumab	[redacted]	[redacted]	Dominant	-£4,363
	BSC	[redacted]	[redacted]	£14,127	£1,683
Scenario 12: Utilities pooled across treatments (except NR)	Secukinumab	[redacted]	[redacted]	Dominant	-£4,194
	BSC	[redacted]	[redacted]	£10,897	-£1,547
Scenario 14: Weight utilities by proportion receiving adalimumab in initial treatment period.	BSC	[redacted]	[redacted]	£2,200	-£1,405
	Secukinumab	[redacted]	[redacted]	£12,403	-£41
Scenario 16: Re-weight surgery costs as per TA935.	Secukinumab	[redacted]	[redacted]	£5,134	£1,529
	BSC	[redacted]	[redacted]	£15,347	£2,903
EAG base case 1	**Secukinumab**	[redacted]	[redacted]	**£61,507**	**£57,902**
	BSC	[redacted]	[redacted]	**£145,930**	**£133,486**

Table 2 Summary of EAG preferred assumptions (EAG base case 2)

Scenario	Bimekizumab vs	Inc. cost	Inc. QALYs	ICER	Change from company base case
Company's base case (uncorrected)	Secukinumab	[redacted]	[redacted]	£3,605	-
	BSC	[redacted]	[redacted]	£12,444	-
EAG-corrected company base case	Secukinumab	[redacted]	[redacted]	£2,200	-£1,405
	BSC	[redacted]	[redacted]	£12,437	-£7
Scenario 2: Replace adalimumab in BSC with discontinued active treatment.	Secukinumab	[redacted]	[redacted]	£79	-£3,526
	BSC	[redacted]	[redacted]	£8,644	-£3,800
Scenario 3: 70-year time horizon.	Secukinumab	[redacted]	[redacted]	£2,213	-£1,392
	BSC	[redacted]	[redacted]	£12,434	-£10
Scenario 5: Use transition probabilities based on the NMA to represent the effectiveness of BSC (Week 16+)	Secukinumab	[redacted]	[redacted]	£56,647	£53,042
	BSC	[redacted]	[redacted]	£122,804	£110,360
Scenario 6: Apply BSC maintenance transition probabilities to patients discontinuing active treatments	Secukinumab	[redacted]	[redacted]	£67,897	£64,292
	BSC	[redacted]	[redacted]	£249,940	£237,496
Scenario 8: SNR stopping rule of 20% per cycle in non-response HS.	Secukinumab	[redacted]	[redacted]	£25,602	£21,997
	BSC	[redacted]	[redacted]	£17,677	£5,233
Scenario 11: Apply adjusted SMR of 1.48 regardless of response level.	Secukinumab	[redacted]	[redacted]	£691	-£2,914
	BSC	[redacted]	[redacted]	£13,287	£843
Scenario 12: Utilities pooled across treatments (except NR)	Secukinumab	[redacted]	[redacted]	-£589	-£4,194
	BSC	[redacted]	[redacted]	£10,897	-£1,547
Scenario 14: Weight utilities by proportion receiving adalimumab in initial treatment period.	BSC	[redacted]	[redacted]	£2,200	-£1,405
	Secukinumab	[redacted]	[redacted]	£12,403	-£41
Scenario 15: Include oral candidiasis management costs.	Secukinumab	[redacted]	[redacted]	£2,214	-£1,391
	BSC	[redacted]	[redacted]	£12,445	£1
Scenario 16: Re-weight surgery costs as per TA935.	Secukinumab	[redacted]	[redacted]	£5,134	£1,529
	BSC	[redacted]	[redacted]	£15,347	£2,903
EAG base case 2	**Secukinumab**	[redacted]	[redacted]	**£63,909**	**£60,303**
	BSC	[redacted]	[redacted]	**£122,330**	**£109,886**

Table 3 EAG's alternative probabilistic base-case analysis results (pairwise)

Technology	Total		Incremental		ICER	NHB @ 20k
	Costs	QALYs	Costs	QALYs		
EAG base case 1						
Best Supportive Care	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£66,971	-0.15
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£156,712	-0.69
EAG base case 2						
Best Supportive Care	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£60,637	-0.27
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£121,264	-0.92

EXTERNAL ASSESSMENT GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report presents a critique of the company's submission to NICE on the clinical and cost-effectiveness of bimekizumab (Bimzelx®) for treating moderate to severe hidradenitis suppurativa (HS).

Bimekizumab received European Medicines Agency (EMA) marketing authorisation in April 2024, for moderate to severe HS in adults who do not have an adequate response to conventional systemic therapy. Bimekizumab does not currently have a marketing authorisation in the United Kingdom (UK) for treating HS.

2.2 Background

2.2.1 Hidradenitis suppurativa

The company's description of hidradenitis suppurativa (HS) is broadly appropriate and relevant to the decision problem. This is presented in Section B.1.3.1 of the company submission (CS). The EAG presents a brief summary of the disease and its treatment here.

HS is a disorder of skin follicles, characterised by recurrent nodules and abscesses in skin folds, predominantly the armpits, groin, buttocks and other intimate areas. As the condition progresses, there is a development of draining tunnels, scarring and reduced mobility. HS tends to begin during puberty, and most people are diagnosed in their twenties or thirties. HS is more common in people with an African-Caribbean background and occurs at a rate three times higher in women than men.

Symptoms may include pain, itching, foul-smelling discharge, and restricted movement of the limbs. These symptoms may lead to low self-esteem, impairment of social functioning, sexual dysfunction, physical deconditioning, inability to carry out activities of daily living, fatigue, sleep disorders, anxiety, and depression. HS is also associated with an increased mortality risk, but this effect is reduced after adjustment for factors such as smoking or body mass index (BMI). Increased mortality may therefore be mostly due to comorbidities such as obesity, and less a direct result of the disease processes.

HS is described by the company as affecting 0.8% of the UK population, which the EAG's clinical advisor considered to be a realistic estimate. The 0.8% estimate corresponds to approximately 435,000 people with HS in England. Real-world data from Europe and the United States suggest that

45.3% have moderate to severe disease, despite treatment.[1] During the clarification stage the company stated that the prevalence of adult HS patients with moderate to severe disease is estimated at 0.28%, of which it is estimated that only 2,456 would be considered for bimekizumab.

2.2.2 Burden of disease

The company's description of the burden of HS (reported in Section B.1.3.1.4 of the CS) appears broadly appropriate and relevant to the decision problem. The EAG presents a brief summary of the burden of disease here.

HS symptoms, particularly pain and malodorous discharge, can lead to social, functional, sexual and mental difficulties, which adversely affect patients' quality of life. Reductions in quality of life increase with disease severity, and are reported to be worse than those observed in many skin diseases, on a par with those observed in rheumatoid arthritis, chronic obstructive pulmonary disease, cancer and cardiovascular disease. There are also reductions in the quality of life of family members, through physical, economic and psychosocial effects. In addition, there is a notable burden on the NHS, with direct annual costs per patient reaching £4,900. Societal effects are also significant, partly due to the NHS burden, but also due to the impact on work and productivity; the OHE (Office of Health Economics) estimated in 2023 that HS has an aggregate annual cost to the UK of £3.8 billion.

2.2.3 Bimekizumab

The company's description of the technology, bimekizumab, (reported in Section B.1.3.2 of the CS) is broadly clear and appropriate.

Bimekizumab is a humanised immunoglobulin G1 (IgG1)/k monoclonal antibody that binds to interleukin (IL)-17A homodimers, IL-17F homodimers and IL-17A/F heterodimers. It is indicated for the treatment of active, moderate to severe HS in adults with an inadequate response to conventional systemic therapy. For this assessment, bimekizumab is proposed only for patients for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment.

The recommended adult dose for treating moderate to severe HS is 320 mg every 2 weeks (Q2W) up to week 16 and every 4 weeks (Q4W) after that.

2.2.4 Clinical pathway of care

Section B.1.3.3 of the CS describes the recommended management of HS, based on UK guidelines; therefore, this is reflective of current UK practice.

2.2.4.1 Diagnosis and classification

Section B.1.3.1.2 of the CS describes the diagnosis and classification of HS. The severity of HS may be classified by the Hurley staging system. Stage I (mild) tends to involve one or a few locally isolated abscesses, without tunnelling or scarring. Stage II (moderate) involves recurrent and more widely spaced abscesses, with the development of tunnels and scars. Stage III (severe) involves more diffuse involvement than stage II, or the existence of multiple interconnecting abscesses and tunnels. Because there may be diagnostic delays lasting up to 10 years, a significant proportion of patients may be at moderate or severe stages of the disease at diagnosis. This delay may have an impact on treatment success, since it is believed that earlier stages of disease are more amenable to treatment.

2.2.4.2 Current standard of treatment

UK guidelines have been published by the British Association of Dermatologists (BAD)[2] and the Primary Care Dermatology Society (PCDS).[3] Treatment may begin with topical antibiotics and antiseptics, alongside lifestyle advice on weight loss and smoking cessation. If this does not lead to adequate resolution, oral tetracyclines may be used for 12 weeks, followed by oral clindamycin and rifampicin if necessary. Retinoids may be considered if previous therapies have been unsuccessful. These approaches constitute "best supportive care".

If these are unsuccessful then biologics may be prescribed. Adalimumab was recommended by NICE in 2016 as an option for treating active moderate to severe HS in adults whose disease has not responded to conventional systemic therapy.[4] In 2023, secukinumab was recommended by NICE as an option for treating active moderate to severe HS in adults when it has not responded well enough to conventional systemic treatment, only if adalimumab is not suitable, did not work or has stopped working.[5]

2.2.5 Intended positioning of bimekizumab

The company has proposed that bimekizumab should be offered after adalimumab if that has proved ineffective, or where adalimumab is contraindicated or unsuitable. This is the same as the current positioning of secukinumab (Figure 3 of the CS). Bimekizumab is not being recommended as an alternative to adalimumab because bimekizumab is not thought by the company to be as cost effective as adalimumab, owing to the availability of low cost adalimumab biosimilars.

The EAG believes that the company's positioning of bimekizumab in the treatment pathway is appropriate.

2.2.6 Equality considerations

As stated in Section B.1.4 of the CS, the EAG notes that HS is more common among women than men, and among people with an African-Caribbean background compared with those with a European background.

The EAG agrees with the company that the use of bimekizumab should not lead to any concerns relating to equity or equality.

2.3 Critique of company's definition of decision problem

A summary and critique of the decision problem addressed in the CS is provided in Table 1. The following sections provide a more detailed critique of each aspect of the decision problem.

2.3.1 Population

The population addressed in the CS differs from the NICE scope, by restricting consideration to people who have failed to respond (or stopped responding) to adalimumab, or for whom adalimumab is contraindicated. The company judges that bimekizumab cannot be a more cost-effective first line treatment than adalimumab, owing to the much lower cost of adalimumab biosimilars.

Based on clinical advice, the EAG agrees that bimekizumab is only likely to be used in the narrower population preferred by the company.

The EAG notes, however, the BE HEARD trials and trial evidence presented in the CS had a predominantly "biologic-naïve" population (81.2%). This differs from the company's preferred population. These issues will be covered in more detail in later sections.

2.3.2 Intervention

The EAG agrees that the intervention is in line with the NICE scope and the proposed dose is in line with the anticipated marketing authorisation.

2.3.3 Comparators

The EAG agrees with the decision to narrow the comparators to secukinumab and best supportive care (BSC) on the basis that it concurs with the prior decision to position bimekizumab as second line therapy after adalimumab.

The company also states that BSC in the decision problem may include "some adalimumab use due to limited treatment options". Given that the decision problem population are defined as a group for whom adalimumab is ineffective or unsuitable, this does not appear to be an appropriate option. The company explained that continuation of adalimumab after failure to reach a Hidradenitis Suppurativa

Clinical Response (HiSCR) landmark is quite common in clinical practice, on the basis that there might be few other alternatives and that adalimumab would continue to exert a small benefit. However, this is contrary to NICE guidance on the use of adalimumab, in which treatment should only be continued beyond 12 weeks if there is clear evidence of response (i.e. HiSCR25).

2.3.4 Outcomes

The outcomes presented in the CS appropriately reflect those listed in the final scope. The company did not report data on disease progression or inflammation and fibrosis. In the clarification response, the company explained that they were not collected in the BE HEARD trials.

Table 4 Summary of decision problem (based on Table 1 in CS)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with moderate to severe HS	Adults with active moderate to severe HS who have an inadequate response to conventional systemic treatments and for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment	This position optimises the cost effectiveness of bimekizumab	The EAG agrees with the narrowing of the decision problem population relative to the NICE scope population. The EAG agrees that bimekizumab is most likely to be used where adalimumab has been ineffective, or where it is contraindicated. The EAG notes that the BE HEARD trial populations differ from the decision problem population. The overall trial populations are predominantly biologic-naïve, whereas the decision problem population is predominantly biologic-experienced. At the clarification stage, the company provided additional results for the biologic-experienced subgroup.
Intervention	Bimekizumab	Bimekizumab Q2W to week 16, followed by bimekizumab Q4W		The bimekizumab dose is in line with the anticipated marketing authorisation and is therefore appropriate.
Comparator(s)	Adalimumab Secukinumab (where adalimumab is not suitable, did not work or has stopped working) Best supportive care (BSC)	Secukinumab Best supportive care (including some adalimumab use due to limited treatment options; assumed to be used by 20.8% of patients on BSC in the cost-effectiveness model)	Bimekizumab is anticipated to be positioned in the UK for people with moderate to severe HS for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment. Therefore, adalimumab is not a directly relevant comparator.	The EAG agrees with the comparators listed in the decision problem; if bimekizumab is positioned as a second line biologic after adalimumab, it would be inappropriate to use adalimumab as a comparator. Adalimumab was included as a part of BSC, on the basis that even if the patient has failed to achieve HiSCR25 on adalimumab, there might still be a small benefit from it, however, this is contrary to NICE guidance on adalimumab.
Outcomes	Disease severity Disease progression Clinical response Inflammation and fibrosis Discomfort and pain Adverse effects of treatment Health-related quality of life	Disease progression, clinical response, and discomfort and pain, assessed as HiSCR25, HiSCR50,[a] HiSCR75, HiSCR90 and HiSCR100 responses, HS lesion counts, IHS4, IHS4-55 responses, flare, the HSSDD and the HSSQ. Adverse effects of treatment, including TEAEs of interest. Health-related quality of life, assessed with the DLQI, HiSQOL and EQ-5D-3L		The outcome measures used in the BE HEARD trials appear to be appropriate. Disease progression and inflammation and fibrosis are present in the NICE scope but not addressed in the company submission, as they were not measured in the BE HEARD trials.

BSC, best supportive care; DLQI, Dermatology Life Quality Index; EAG, External Assessment Group; EQ-5D-3L, 3-level, 5-dimension EuroQol questionnaire; HiSCR, Hidradenitis Suppurativa Clinical Response; HiSQOL, Hidradenitis Suppurativa Quality of Life; HS, hidradenitis suppurativa; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary; HSSQ, Hidradenitis Suppurativa Symptom Questionnaire; IHS4, International Hidradenitis Suppurativa Severity Score System; IHS4-55, 55% reduction in IHS4 total score; NICE, National Institute for Health and Care Excellence; Q2W, every 2 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse events.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review to identify all relevant clinical evidence relating to the efficacy and safety of bimekizumab, adalimumab and secukinumab in the treatment of moderate to severe HS. Details of the review are reported in Appendix D of the CS.

3.1.1 Searches

Appendix D of the CS contained details of the company searches to identify clinical evidence on bimekizumab, adalimumab and secukinumab in the treatment of moderate to severe HS.

Overall, the searches were of reasonable quality. However, it is unclear how adequate they were for retrieving all relevant randomised controlled trials (RCTs) from MEDLINE and Embase for the period April 2023 to October 2023. In addition, as the database searches were designed to identify RCTs, it is possible that they may have missed any relevant systematic reviews or network meta-analyses of treatments for HS. An additional search of databases of systematic reviews would have been appropriate for this review. Finally, a limit to English language studies was applied to all searches of MEDLINE, Embase and the October 2023 searches of CENTRAL, therefore language bias is a possibility.

The full EAG appraisal of the searches can be found in Table 5.

Table 5 EAG appraisal of evidence identification

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	Some of the wording to describe the search strategies was unclear and search strategies for conference abstracts and websites were missing from the CS. However, these reporting issues were resolved in the company response to the EAG's clarification questions.
Were appropriate sources searched?	PARTLY	Primary studies were sought from key databases, sources of published and unpublished healthcare literature and reference checking. However, there was limited searching for previous systematic reviews – the Cochrane Database of Systematic Reviews, Epistemonikos, KSR Evidence and DARE were not searched.
Was the timespan of the searches appropriate?	YES	- Databases: inception to October 2023. - Conference abstracts (6 named conferences): 2020-2023. - Clinical trial registers and websites: all available years to November 2023
Were appropriate parts of the PICOS included in the search strategies?	YES	**Oct 2023 search:** *Population* (HS) AND *Study design* (RCTs). **April 2023 search:** *Population* (HS) AND *Interventions* (bimekizumab OR secukinumab OR adalimumab) AND *Study design* (RCTs).

Were appropriate search terms used?	PARTLY	**Database searches** - Terms for the population and interventions were appropriate. - The April 2023 searches of MEDLINE and Embase included a wide variety of search terms for identifying RCTs. However, the October 2023 searches used a less comprehensive set of RCT terms (based upon RCT filters by the Scottish Intercollegiate Guidelines Network [SIGN]), running the risk of missing RCTs for the period April 2023 to October 2023. - Search terms to identify systematic reviews were not used in either the April 2023 or October 2023 searches of MEDLINE and Embase. **Conference abstracts** - Some of the search strategies used to identify conference abstracts did not include search terms for either HS or the interventions bimekizumab, secukinumab or adalimumab, so would not have retrieved conference abstracts of relevance for this review. **Clinical trial registers and website searches** - Appropriate search terms were used.
Were any search restrictions applied appropriate?	NO	A limit to English language studies was applied in all searches of MEDLINE, Embase and the October 2023 search of CENTRAL. Therefore, language bias is a possibility.
Were any search filters used validated and referenced?	PARTLY	The company clarified in their response to the EAG's clarification questions that RCT search filters from SIGN were included within the October 2023 and April 2023 MEDLINE and Embase search strategies. Externally validated RCT search filters with higher sensitivity than the SIGN RCT filters are available and would have been a more appropriate choice, particularly for the October 2023 searches of MEDLINE and Embase.[6, 7]
CS, company submission; EAG, external assessment group; HS, hidradenitis suppurativa; PICOS, population, intervention, comparator, outcomes, study type; RCT, randomised controlled trial; SIGN, Scottish Intercollegiate Guidelines Network.		

3.1.2 Inclusion criteria

The eligibility criteria used to select studies for inclusion in the systematic review were presented in Table 83 (Appendix D) of the CS. Eligibility criteria relating to the population were broader than the decision problem addressed in the CS and included all adult patients with HS, with no restriction to 'moderate to severe HS' or patients with 'an inadequate response to conventional systemic treatments and for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment'. The interventions of interest were bimekizumab, secukinumab and adalimumab and the comparators were biological therapies, surgery and placebo. Studies of treatments used as 'best supportive care' were not sought. A range of outcomes and specific outcome measures were listed, which appear appropriate. RCTs and open-label extension studies were eligible for inclusion.

Study selection was undertaken independently by two reviewers, with disagreements resolved through discussion or arbitration by a more senior reviewer, minimising the possibility of errors or bias affecting the study selection process. The EAG reviewed the tables of studies excluded at full-text screening stage (Tables 86 and 87 in Appendix D of the CS) and did not identify any inappropriate exclusions.

Eleven unique RCTs were included in the systematic review and assessed for inclusion in the network meta-analysis (NMA). Treatments included in the NMA were restricted to doses and schedules with marketing authorisation (or anticipated marketing authorisation in the case of bimekizumab), which resulted in two RCTs and one treatment arm of a third RCT being excluded from the NMA. The main sources of clinical effectiveness evidence on bimekizumab were the BE HEARD I and BE HEARD II RCTs.[8] Additional data were included from the BE HEARD EXT extension study and a phase 2 RCT (HS0001).[9]

3.1.3 Data extraction

Data extraction was undertaken by one reviewer and independently checked by a second reviewer, minimising the possibility of errors or bias affecting the data extraction process. Information on the design and methods of the BE HEARD trials, along with baseline characteristics of trial participants, is presented in the CS, with supplementary information presented in Appendix D. Results of the BE HEARD trials are presented in Section B.2.6 of the CS, with subgroup analysis results presented in Section B.2.7. At the clarification stage, the EAG requested additional information, including separate baseline characteristics and results for the subgroup of biologic-experienced patients in the BE HEARD trials, which were provided by the company.

Brief study details and baseline characteristics of participants in the nine RCTs included in the overall cohort NMA are presented in Appendix D of the CS. At the clarification stage, the company provided useful additional information on studies included in the NMA, along with separate baseline characteristics for the subgroup of biologic-experienced patients in each study.

3.1.4 Quality assessment

Risk of bias was assessed using the Cochrane risk of bias tool for RCTs,[10] which was appropriate. Risk of bias assessment was undertaken by one reviewer and independently checked by a second reviewer, minimising the possibility of errors or bias. The risk of bias assessment results for each of the nine studies included in the NMA are presented in Table 115 (Appendix D) of the CS.

Eight RCTs were considered to have a low overall risk of bias and one RCT (SHARPS) was considered to have ‘some concerns’ owing to the selection of the reported result, as authors performed unplanned post hoc analyses. At the clarification stage, the EAG queried the apparent inconsistency in the critical appraisal of the trials, since data from the BE HEARD trials were also from unplanned post hoc analyses, rather than the prespecified analysis plan. Results from the prespecified analysis were presented in Appendix D of the CS, rather than the main results section. The company’s response highlighted additional concerns relating to the analyses in the SHARPS trial and reiterated

that the post hoc analyses of the BE HEARD studies align closer with real world practice and reduce heterogeneity in the network to allow for indirect comparison with secukinumab evidence.

The EAG also has some concerns with possible imbalance in the BE HEARD trials between treatment arms and the risk of performance bias, owing to bimekizumab and placebo injections looking different. The company explained that the use of a placebo injectate with the same colour as the bimekizumab solution was not possible without using non-inert components. The EAG accept this rationale, but considers that an unblinded person performing injections could cause performance bias through preferential treatment of one group during the injection procedure (such as different levels of verbal or non-verbal communication), or through inadvertent unblinding of the patient.

3.1.5 Evidence synthesis

Results of the BE HEARD I and BE HEARD II trials were pooled; although some results were presented from the individual trials, rather than the pooled results.

The company conducted a network meta-analysis (NMA) to estimate the relative efficacy of bimekizumab, secukinumab and placebo at week 12 or 16, see Section 3.9 for details. In addition, an unanchored matching-adjusted indirect comparison (MAIC) of bimekizumab versus secukinumab at weeks 48-52 was conducted, see Section 3.10 for details.

3.2 Studies of the clinical efficacy and safety of bimekizumab

Three RCTs relevant to bimekizumab were found by the systematic review: BE HEARD I,[8, 11] BE HEARD II[8, 12] and HS0001.[9] An observational study by Becherel and colleagues was also found.[13] Only the RCT data have been included in the NMA analyses (see Section 3.9).

The company's efficacy and safety data were primarily based on the BE HEARD I and BE HEARD II RCTs.[8, 11, 12] BE HEARD I and II were methodologically identical and have therefore been described together. Long-term (week 96) data on treatment response and safety, from the BE HEARD EXT open-label extension study,[14, 15] are presented in Section B.2.6.10 and Section B.2.10.3 of the CS, respectively. A detailed description of the methodology and results of HS0001[9] and the observational study[13] was not included in the CS, and so only brief details are provided in this report.

The EAG notes that the two BE HEARD trials were predominately in patients with no prior exposure to adalimumab (termed "biologic-naïve" here and in the CS). Only a subset of patients had previously received adalimumab or other biologic therapies for HS (termed "biologic-experienced" here and in the CS).

Because the proposed target population is "patients for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment" the EAG believes that the biologic-naïve subgroup is of limited relevance to this report, and therefore we focus our presentation of results on the biologic-experienced subgroup. We note that this is not exactly the target population either, because it includes a small number of patients who received biologics other than adalimumab, and may not include those patients for whom adalimumab was unsuitable.

3.3 The BE HEARD trials

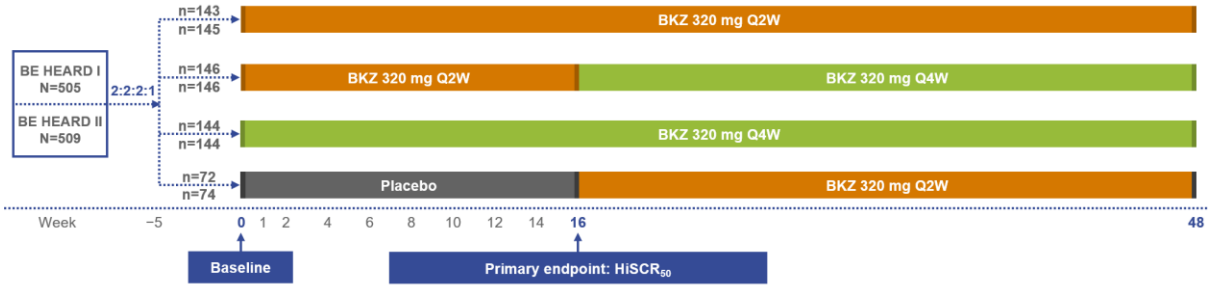
3.3.1 Trial design

BE HEARD I and II were identically designed double-blind phase 3 RCTs.[8, 11, 12] Patients were randomly allocated to four groups (summarised in Figure 1):

1. bimekizumab 320 mg every two weeks, 0-48 weeks ("Q2W/Q2W" arm)
2. bimekizumab 320 mg every two weeks 0-16 weeks, followed by bimekizumab 320 mg every four weeks ("Q2W/Q4W" arm)
3. bimekizumab 320 mg every four weeks, 0-48 weeks ("Q4W/Q4W" arm)
4. placebo 0-16 weeks followed by bimekizumab 320 mg every two weeks

Concomitant treatments permitted in all arms included doxycycline, minocycline, or an equivalent systemic tetracycline if a patient was already on a stable dose 28 days before baseline. Wound dressings were also allowed, but this was limited to alginates, hydrocolloids, and hydrogels. Stable doses of non-opioid analgesics were also permitted where needed.

Figure 1 BE HEARD I and II study design (from CS Figure 4)



BKZ = Bimekizumab; Q2W = every two weeks; Q4W = every 4 weeks.

The recommended dose for treating moderate to severe HS is 320 mg every two weeks up to week 16, followed by a maintenance dose of 320 mg every four weeks. One of the arms of the BE HEARD trials reflects this longer-term dosing schedule. Because all patients in the placebo group transferred to bimekizumab after 16 weeks, data relating to the 16–48-week section of the trials are no longer part of

a placebo comparison. Therefore, the two groups randomised to bimekizumab 320 mg every two weeks for the first 16 weeks ("Q2W/Q2W" and "Q2W/Q4W" arms) are relevant to the decision problem for comparing bimekizumab with placebo up to 16 weeks.

At 48 weeks, patients were invited to transfer to an open label extension study (BE HEARD EXT). Any patients that had obtained an HiSCR90 response during the maintenance period (calculated using the average lesion count from weeks 36, 40 and 44) were given bimekizumab 320 mg Q4W, and those who had not achieved this response were given bimekizumab 320 mg Q2W.

The outcomes assessed in the BE HEARD trials and presented in the CS are shown in Table 6 below. HiSCR50 was the primary outcome, all others were secondary outcomes.

Table 6 BE HEARD trial outcome measures presented in the company submission

Outcome	NICE scope equivalent (as determined by company in Table 7, CS)	Description of event (binary outcomes) or measure (continuous outcomes)	Outcome type	Timepoints of trial where measured
HiSCR50	Clinical response	50% reduction from baseline in the total abscess/nodule count, with no increase from baseline in abscess or draining tunnel count	Binary (higher proportion with event better)	16 weeks, 48 weeks, 96 weeks
HiSCR75		75% reduction from baseline in the total abscess/nodule count, with no increase from baseline in abscess or draining tunnel count		16 weeks, 48 weeks, 96 weeks
HiSCR100		100% reduction from baseline in the total abscess/nodule count, with no increase from baseline in abscess or draining tunnel count		16 weeks, 48 weeks, 96 weeks
HiSCR90		90% reduction from baseline in the total abscess/nodule count, with no increase from baseline in abscess or draining tunnel count		16 weeks, 48 weeks, 96 weeks
HiSCR25		25% reduction from baseline in the total abscess/nodule count, with no increase from baseline in abscess or draining tunnel count		16 weeks
Change from baseline in AN count	Disease Severity	Percentage change from baseline in abscess and inflammatory nodule count	Continuous (lower better; i.e. negative change = improvement)	16 weeks, 48 weeks
Absolute change in DT count		Absolute change from baseline in draining tunnel count	Continuous (lower better; i.e. negative change = improvement)	16 weeks, 48 weeks
> 3 DT reduction		Achievement of > 3 draining tunnel reduction, in participants with >5 draining tunnels at baseline	Binary (higher proportion with event better). Note the sample is restricted to participants with >5 DTs at baseline so analysis not based on the randomised samples	16 weeks, 48 weeks
IHS4		Achievement of mild rating on International Hidradenitis Suppurativa (IHS) Severity Score. The score is calculated as 1 x the number of nodules plus 2 x the number of abscesses plus 4 x the number of draining tunnels. Scores ≤ 3 indicate mild HS, 4–10 moderate HS, and ≥ 11 severe HS	Binary (higher proportion with event better)	16 weeks, 48 weeks, 96 weeks
IHS4-55		Achievement of 55% reduction in IHS4 total score	Binary (higher proportion with event better)	16 weeks, 48 weeks, 96 weeks
Flare		Attaining at least a 25% increase in abscess and inflammatory nodule count with an absolute increase of ≥ 2 abscess and inflammatory nodules relative to baseline	Binary (lower proportion with event better)	16 weeks, 48 weeks

Change from baseline in NRS worst skin pain	Discomfort and Pain	Absolute change from baseline in numerical rating scale for worst skin pain score was assessed using the "worst skin pain" item (11-point NRS) in the Hidradenitis Suppurativa Symptom Daily Diary (HSSDD).	Continuous (lower better; i.e. negative change = improvement)	16 weeks
HSSDD worst skin pain NRS response		Achieving at least a 3-point decrease from baseline in HSSDD weekly worst skin NRS pain score (regarded as the threshold for clinically meaningful change) among study participants with a score of ≥ 3 at baseline.	Binary (higher proportion with event better)	16 weeks
NRS30		Achieving ≥ 30% reduction and reduction of ≥ 2 units from baseline in HSSDD weekly worst skin pain NRS score, assessed in patients with a baseline NRS score of ≥ 3	Binary (higher proportion with event better). Note the sample is restricted to participants with baseline NRS score of ≥ 3 so analysis not based on the randomised samples	16 weeks
HSSQ 0		Achieving HS symptom questionnaire zero response (score of 0), among patients with baseline scores ≥ 1	Binary (higher proportion with event better). Note the sample is restricted to participants with baseline scores ≥ 1 and so analysis not based on the randomised samples.	16 weeks, 48 weeks
DLQI	Health-related Quality of Life	Dermatology Life Quality Index change from baseline	Continuous (lower better; i.e. negative change = improvement)	16 weeks, 48 weeks
DLQI MCID response		Achievement of a ≥ 4-point improvement (deemed the minimal clinically important difference response) among patients with baseline scores ≥ 4 in DLQI	Binary (higher proportion with event better). Note the sample is restricted to participants with baseline scores ≥ 4 in DLQI and so analysis not based on the randomised samples.	16 weeks, 48 weeks
HiSQOL		Change from baseline for Hidradenitis Suppurativa Quality Of Life total score, and each of the following constituent domains: symptoms, psychological and activities-adaptation	Continuous (lower better; i.e. negative change = improvement)	16 weeks, 48 weeks
EQ-5D-3L		5-dimension, 3-level EuroQol questionnaire score	Continuous (higher score better)	16 weeks, 48 weeks

AN, abscess and inflammatory nodule; CS, company submission; DLQI, Dermatology Life Quality Index; DT, draining tunnel; EQ-5D-3L, 3-level, 5-dimension EuroQol questionnaire; HiSCR, Hidradenitis Suppurativa Clinical Response; HiSQOL, Hidradenitis Suppurativa Quality of Life; HS, hidradenitis suppurativa; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary; HSSQ, Hidradenitis Suppurativa Symptom Questionnaire; IHS4, International Hidradenitis Suppurativa Severity Score System; IHS4-55, 55% reduction in IHS4 total score; MCID, minimal clinically important difference; NICE, National Institute for Health and Care Excellence; NRS, numerical rating scale.

3.3.2 Statistical analysis

The 16-week and 48-week efficacy analyses were performed in two main ways: using observed cases only (OC) or the randomised set (RS), which included all randomised patients. For the RS analyses, missing data were accounted for by two imputation methods:

1) Missing data for continuous outcomes were imputed using multiple imputation (MI) with the Markov Chain Monte Carlo (MCMC) method,
2) Missing data for binary outcomes were imputed using modified non-responder imputation (mNRI).

The EAG agreed that the methods used were appropriate.

Participants who experienced an intercurrent event were treated as missing at subsequent visits, and the imputation methods described above were applied. Intercurrent events were originally defined as discontinuation due to lack of efficacy, discontinuation due to adverse events and antibiotic use for any reason (if this antibiotic use was newly initiated on or after the baseline visit). This was called the "all-ABX" approach in the CS. The company made a post hoc decision to change the third criterion to "antibiotic use solely related to HS rescue therapy" as determined by the principal investigator. This was called the "HS-ABX" approach in the CS. The company states that this was to increase the clinical relevance of the trial data; antibiotics used for other conditions, or for non-rescue therapy in HS, do not indicate a failure of treatment and therefore should not be regarded as an intercurrent event. The EAG agrees that using this "HS-ABX" approach to imputation was reasonable for this assessment.

A hierarchical testing procedure was used for the all-ABX dataset, which is described in the CS in Section B.2.4.4 and Figure 5. However, this was not used with the HS-ABX data presented in the CS and this report because statistical testing was deemed inappropriate for a post hoc analysis approach.

Safety analyses were conducted using the safety set (SS), including all study participants receiving at least one full or partial dose of bimekizumab or placebo, and the active medication set (AMS), including all study participants receiving at least one full or partial dose of bimekizumab only.

3.3.3 Patient characteristics

Participants were adults with a diagnosis of moderate or severe HS for at least six months, with an inadequate response to systemic antibiotics. Patients with more than 20 draining tunnels at baseline were excluded. Table 8 in the CS summarises the BE HEARD I and II inclusion and exclusion criteria. The EAG clinical expert agreed that the eligibility criteria appear appropriate, but the EAG sought clarification from the company on why patients with more than 20 draining tunnels at baseline

were excluded. The company explained that this was consistent with the PIONEER and SUNRISE/SUNSHINE trials. The rationale of this exclusion criterion is to facilitate HiSCR measurement, which requires assessment of draining fistulas. Because such assessment is complex, limiting the number of draining fistulas may be useful.

Patients were recruited to the BE HEARD trials from North America, Europe, Australia, Israel, Turkey and Japan. Five patients from the UK were recruited to BE HEARD II, but it is unclear whether any of these patients were in the biologic-experienced subgroup.

Baseline characteristics of the trials are summarised in Table 7 (from Table 11 of the CS). However, these were not in the decision problem population of biologic-experienced patients, but in a population that was predominantly biologic-naïve. On request, the company also supplied data on baseline characteristics in patients who were biologic-experienced (Table 7). The Q4W/Q4W arm of the BE HEARD trials is not presented here as it is not the recommend dose up to 16 weeks.

The EAG notes numerical differences in gender, current and former smoking, race, duration of illness and IHS4 score between the bimekizumab and placebo groups in the biologic-experienced subgroup. The company provided a clear description of the randomisation process, which confirmed that such differences were likely due to chance. Nevertheless, some of the between arm differences may have conferred an advantage to the bimekizumab arm.

There were also differences in the baseline characteristics between the overall population and the biologic-experienced population, namely: current and former smoking status, Hurley stage, DT count, IHS4 score, HISQOL score and DLQI score. In general, biologic-experienced patients had more severe disease and poorer quality of life than biologic-naïve patients.

The company clarified that the main biologic previously used in the BE HEARD trials was adalimumab (22.4% BE HEARD I, 12.3% BE HEARD II), followed by infliximab (5.2% BE HEARD I, 1.8% BE HEARD II), with very small numbers for other biologic agents. The company did not have data on the number contraindicated for adalimumab, nor the numbers with primary and secondary failure.

Table 7 Baseline characteristics of the combined Q2W/Q2W and Q2W/Q4W bimekizumab arms and the placebo arm in overall population and biologic-experienced subgroups (Table 11, CS and Table 9, company response to clarification)

	BE HEARD I (overall trial population)		BE HEARD II (overall trial population)		POOLED (Biologic-experienced subgroup)	
Category	**Placebo n = 72**	**BKZ n = 289**	**Placebo n = 74**	**BKZ n = 291**	**Placebo n = 29**	**BKZ n = 115**
Age, years, mean ± SD	36.4 ± 12.4	36.9 ± 12.4	38.1 ± 13.2	36.9 ± 12.3	39.5 ± 12.1	38.6 ± 13.3
Female	44 (61.1)	176 (60.9)	31 (41.9)	150 (51.5)	21 (72.4)	57 (49.6)
Body weight, kg, mean ± SD	94.62 ± 24.81	97.23 ± 25.36	100.28 ± 23.65	95.41 ± 24.22	94.0 ± 27.0	96.7 ± 26.5
BMI, kg/m^2, mean ± SD	32.36 ± 7.77	33.36 ± 8.31	33.81 ± 8.70	32.01 ± 8.04	32.69 ± 8.67	32.11 ± 7.95
Smoking Current	37 (51.4)	127 (43.9)	38 (51.4)	134 (46.0)	18 (62.1)	57 (49.6)
Smoking Former	7 (9.7)	43 (14.9)	10 (13.5)	49 (16.8)	0	26 (22.6)
White	55 (76.4)	233 (80.6)	64 (86.5)	232 (79.7)	23 (79.3)	99 (86.1)
Black	8 (11.1)	41 (14.2)	5 (6.8)	22 (7.6)	4 (13.8)	6 (5.2)
Asian	3 (4.2)	2 (0.7)	5 (6.8)	22 (7.6)	1 (3.4)	2 (1.7)
Duration of disease, years, Mean ± SD	11.51 ± 9.87	8.51 ± 7.62	8.03 ± 8.61	7.35 ± 7.38	10.96 ± 8.58	8.79 ± 7.79
Hurley stage II (derived), n (%)	34 (47.2)	149 (51.6)	45 (60.8)	177 (60.8)	11 (37.9)	42 (36.5)
Hurley stage III (derived), n (%)	38 (52.8)	140 (48.4)	29 (39.2)	114 (39.2)	18 (62.1)	73 (63.5)
AN count, mean ± SD	15.0 ± 11.9	15.3 ± 13.5	13.9 ± 7.8	16.7 ± 15.5	15.66 ± 8.71	16.62 ± 13.51
DT count, mean ± SD	3.2 ± 4.0	4.0 ± 4.9	3.5 ± 3.7	3.6 ± 4.0	5.21 ± 5.62	5.84 ± 5.64
IHS4 score, mean ± SD	30.8 ± 24.3	35.0 ± 30.4	30.4 ± 19.2	34.4 ± 29.7	39.9 ± 25.6	44.6 ± 34.7
HiSQOL total score, mean ± SD	25.89 ± 14.82	25.06 ± 12.95	26.92 ± 13.44	24.22 ± 12.85	28.46 ± 15.17	27.83 ± 12.56
DLQI total score, mean ± SD	12.4 ± 8.0	11.5 ± 6.6	11.9 ± 6.1	10.6 ± 6.5	13.6 ± 8.1	13.0 ± 6.8
Antibiotic use (derived) Yes	5 (6.9)	27 (9.3)	6 (8.1)	30 (10.3)	3 (10.3)	8 (7.0)
Prior biologic use for HS, n (%) Yes	19 (26.4%)	75 (26.0%)	10 (13.5%)	40 (13.7%)	29 (100)	115 (100)

AN, abscess and inflammatory nodule; BKZ, bimekizumab; BMI, body mass index; DLQI, Dermatology Life Quality Index; DT, draining tunnel; HiSQOL, Hidradenitis Suppurativa Quality of Life; HS, hidradenitis suppurativa; IHS4, International Hidradenitis Suppurativa Severity Score System; kg, kilogram; m, metre; n, number; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation.

3.3.4 Patient flow and discontinuations

In the biologic-experienced subgroup, there were 28/115 (24%) discontinuations in the bimekizumab Q2W/Q2W and Q2W/Q4W arms and 6/29 (21%) discontinuations in the placebo arm. Patient discontinuations were most commonly due to withdrawal of consent, lack of efficacy and adverse events (Table 23, company response to clarification).

The EMA assessment report highlighted that the impact of treatment withdrawal or treatment pause was not evaluated in the clinical studies of bimekizumab, despite recommending that it be assessed.[16]

[redacted]

3.3.5 Protocol deviations

In the initial treatment phase, 18.8% patients in BE HEARD I and 16.1% patients in BE HEARD II had important protocol deviations; mostly prohibited concomitant medication use. No information was available on protocol deviations in the biologic-experienced subgroup.

3.4 Clinical findings of the BE HEARD trials

The CS presents a range of results from the BE HEARD trials, but most results related to patients not relevant to this assessment because the overall sample comprised predominantly "biologic-naive" patients who had no prior exposure to adalimumab. The EAG is concerned that results based on predominantly biologic-naïve patients may tend to overestimate benefits in the decision problem population (biologic-experienced patients) because prior failure on one biologic might be expected to increase the risk of subsequent failure on a related biologic.

On request for clarification, the company claimed that the trial results demonstrated equipoise between the two populations,[17] and that this justified the use of the overall (predominantly biologic-naïve) population to represent the target population (biologic-experienced).

The EAG agree that the results to week 16 do not suggest any difference between biologic-experienced and biologic-naïve patients. However, the EAG have chosen to present results primarily for patients who were biologic-experienced, as this most closely matches the target population in the scope.

In addition, results were presented in the CS for those not receiving the intended 2-weekly dose of bimekizumab 320 mg in the first 16 weeks. This report thus also excludes those who received

bimekizumab 320 mg Q4W in the first 16 weeks of the study. Additional results can be found in the CS, and a summary of results from the entire BE HEARD cohort is available in Appendix 1.

There were no subgroup analyses conducted for the biologic-experienced group. Subgroup analyses for the overall (predominantly biologic-naïve) population are described in Appendix E of the CS.

3.4.1 Clinical response outcomes

Table 8 summarises results for the clinical response outcomes in the biologic-experienced subgroup. This shows that bimekizumab is numerically superior to placebo across all clinical response outcomes at 16 weeks.

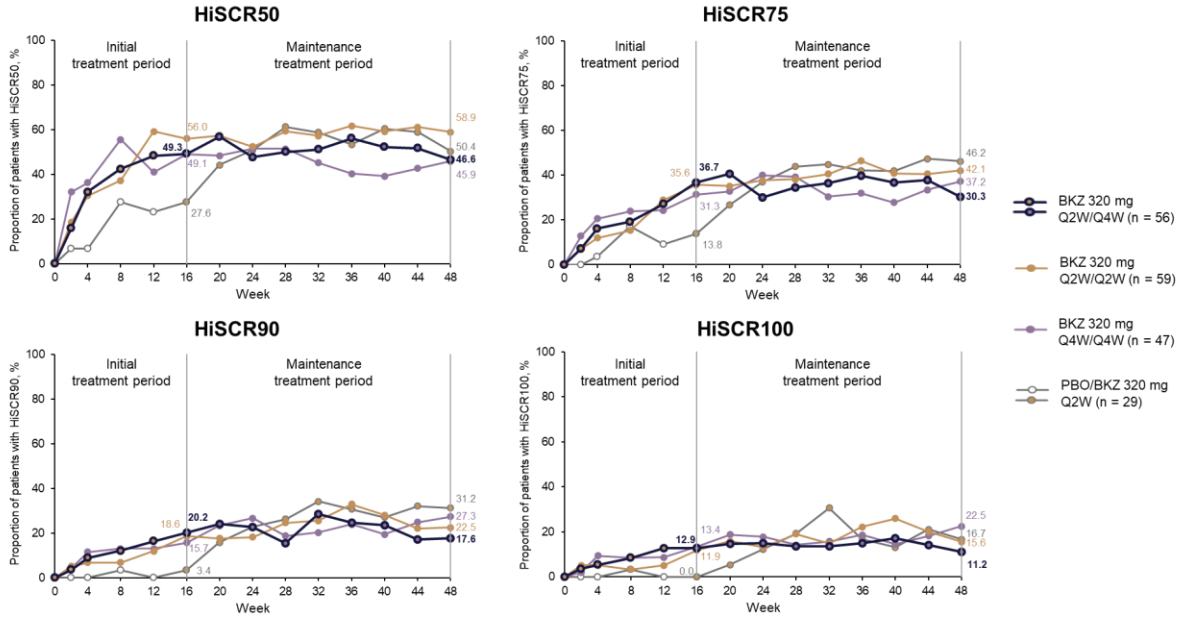
When compared to the results for the overall data (Appendix 1), the proportion of patients achieving a response is lower for the biologic-experienced subgroup than the overall data in both the Q2W/Q2W and Q2W/Q4W groups, and in the placebo group. This difference may be explained by there being a smaller placebo effect in the biologic-experienced population, who may have reduced expectations of treatment success. This suggests that if bimekizumab were to be used in clinical practice for biologic-experienced patients, the outcomes would probably not be as good as the overall population results seen in the BE HEARD trials.

Table 8 Results of the pooled BE HEARD trials at 16 weeks for the clinical response outcomes (biologic-experienced participants only)

Trial outcome	Bimekizumab Q2W/Q2W	Bimekizumab Q2W/Q4W	Placebo
HiSCR50, % (95% CI) [n]	56.0 (43.3, 68.6) [59]	49.3 (36.0, 62.7) [56]	27.6 (NC, NC) [29]
HiSCR75, % (95% CI) [n]	35.6 (NC, NC) [59]	36.7 (23.8, 49.5) [56]	13.8 (NC, NC) [29]
HiSCR25, % (95% CI) [n]	No data provided		
HiSCR90, % (95% CI) [n]	18.6 (NC, NC) [59]	20.2 (9.5, 30.8) [56]	3.4 (NC, NC) [29]
HiSCR100, % (95% CI) [n]	11.9 (NC, NC) [59]	12.9 (4.0, 21.8) [56]	0 (NC, NC) [29]
CI, confidence interval; HiSCR, Hidradenitis Suppurativa Clinical Response; n, number; NC, not calculable; Q2W, every 2 weeks; Q4W, every 4 weeks.			

Figure 2 shows the clinical response levels, in terms of HiSCR, over 48 weeks in the biologic-experienced subgroup. These results suggest that response rates are largely unchanged over the follow-up period from 16 weeks to 48 weeks. In the overall data (Figure 7, CS) there was some evidence that HiSCR response rates continued to increase between weeks 16 and 48. This again suggests that outcomes on bimekizumab in biologic-experienced patients may not be as good as for the overall population in the BE HEARD trials.

Figure 2 HiSCR50, HiSCR75, HiSCR90 and HiSCR100 responses up to week 48 in pooled BE HEARD population for the biologic-experienced subgroup (mNRI for HS-ABX) [Figure 1, company response to clarification)



3.4.2 Disease severity outcomes

Table 9 summarises results for the disease severity outcomes in the biologic-experienced subgroup. This shows that bimekizumab is numerically superior to placebo across all disease severity outcomes at 16 weeks. These results are qualitatively similar to those in the overall cohort (Appendix 1).

Table 9 Results of the pooled BE HEARD trials at 16 weeks for the disease severity outcomes (biologic-experienced participants only)

Trial outcome	Bimekizumab Q2W/Q2W	Bimekizumab Q2W/Q4W	Placebo
AN count percentage change from baseline (SE) [n]	−53.6 (6.2) [59]	−51.4 (6.5) [56]	−11.7 (11.5) [29]
Absolute change in DT count, mean (SE) (95% CI) [n]	−2.6 (0.5) [59]	−2.0 (0.5) [56]	0.0 (0.7) [29]
Proportion with ≥5 DTs at baseline achieving ≥3 DT reduction, % (95% CI) [n]	65.5 (49.0, 82.0) [32]	45.5 (NC, NC) [22]	14.3 (NC, NC) [14]
Proportion with IHS4 ‘mild’ rating (%) [n] [none ‘mild’ at baseline in any group]	No data	15% [56]	3.7% [29]
Proportion with IHS4-55 response % (95% CI) [n]	49.2 (NC, NC) [59]	46.1 (32.8, 59.4) [56]	13.8 (NC, NC) [29]
Proportion of patients with flare at 16 weeks, % (95% CI) [n]	15.3 (NC, NC) [59]	16.5 (6.7, 26.3) [56]	44.8 (NC, NC) [29]
AN, abscess and inflammatory nodule; CI, confidence interval; DT, draining tunnel; IHS4, International Hidradenitis Suppurativa Severity Score System; IHS4-55, 55% reduction in IHS4 total score; n, number; NC, not calculable; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.			

During the 16 to 48-week maintenance phase, in the biologic-experienced subgroup, there was a larger reduction in AN and DT count (CS Tables 11 and 12, company response to clarification

questions). IHS4 severity also demonstrated an increase in benefit, with around 21.6% at 'mild' severity level at 48 weeks in the Q2W/Q4W group (Figure 3, company response to clarification questions). IHS4-55 response was maintained at 48 weeks (Table 13, company response to clarification questions). However, levels of flare increased over the maintenance period, particularly in the Q2W/Q4W dose group (Table 14, company response to clarification questions). On the whole, these results are qualitatively similar to those in the overall cohort (Figures 10-13, CS).

3.4.3 Discomfort and pain outcomes

Table 10 summarises results for the discomfort and pain outcomes in the biologic-experienced subgroup. This shows that bimekizumab is numerically superior to placebo across all discomfort and pain outcomes at 16 weeks. These results are qualitatively similar to those in the overall cohort (Appendix 1).

Table 10 Results of the pooled BE HEARD trials at 16 weeks for discomfort and pain outcomes (biologic-experienced participants only)

Trial outcome	Bimekizumab Q2W/Q2W	Bimekizumab Q2W/Q4W	Placebo
Change from baseline in worst skin pain NRS (SE) [n]	−1.9 (0.3) [115]		−0.5 (0.4) [29]
HSSDD worst skin pain NRS response based on at least a 3-point decrease (95% CI) [n]*	31.8 (21.4, 42.2) [86]		8.2 (0.0, 22.7) [18]
HSSDD worst skin pain NRS response based on 30% reduction and at least 2-point reduction (95% CI) [n]*	44.4 (33.3, 55.4) [86]		20.5 (0.3, 40.7) [18]
Proportion with HSSQ 0 skin response among patients with baseline HSSQ ≥1, % (95% CI) [n]	6.8% (NC, NC) [59]	2.0% (0.0–5.8%) [54]	0.0% (NC, NC) [26]

*Amongst patients with a score ≥3 at baseline.
CI, confidence interval; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary; HSSQ, Hidradenitis Suppurativa Symptom Questionnaire; n, number; NC, not calculable; NRS, numerical rating scale; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.

HSSQ skin pain responses improved substantially from week 16 to week 48 in the biologic-experienced subgroup (Table 18, company response to clarification). These results are qualitatively similar to those in the overall cohort (Figure 14, CS). Longer term results were not provided for the other outcomes; HSSDD was not measured in the maintenance period.

3.4.4 Quality of life outcomes

Table 11 summarises results for the quality of life outcomes in the biologic-experienced subgroup. This shows that bimekizumab is numerically superior to placebo across all quality of life outcomes at 16 weeks. These results are qualitatively similar to those in the overall cohort (Appendix 1).

Table 11 Results of the pooled BE HEARD trials at 16 weeks (imputed, HS-ABX analysis only) for the quality of life outcomes (biologic-experienced participants only)

Trial outcome	Bimekizumab Q2W/Q2W	Bimekizumab Q2W/Q4W	Placebo
Mean change from baseline in DLQI mean (SE) [n]	−5.0 (0.7) [59]	−4.4 (0.8) [56]	−2.9 (1.3) [29]
DLQI MCID response % (95% CI) [n]	60.7 (47.7–73.7) [55]	52.1 (37.5–66.6) [47]	37.5 (NC–NC) [24]
HiSQOL total change from baseline, mean (SE) [n]	-11.2 (1.6) [59]	-10.9 (1.7) [56]	−3.2 (2.5) [29]
HiSQOL symptoms domain change from baseline, mean (SE) [n]	-2.4 (0.4) [59]	-2.7 (0.5) [56]	-0.9 (0.7) [29]
HiSQOL psychosocial domain change from baseline, mean (SE) [n]	-2.3 (0.5) [59]	-1.9 (0.5) [56]	−0.4 (0.7) [29]
HiSQOL activities-adaptation domain change from baseline, mean (SE) [n]	-6.4 (0.8) [59]	-6.3 (0.9) [56]	−2.2 (1.4) [29]
CI, confidence interval; DLQI, Dermatology Life Quality Index; HiSQOL, Hidradenitis Suppurativa Quality of Life; MCID, minimal clinically important difference; n, number; NC, not calculable; Q2W, every 2 weeks; Q4W, every 4 weeks, SE, standard error.			

During the 16 to 48-week maintenance phase, in the biologic-experienced subgroup, there were increased improvements in HiSQOL in all dose groups (Table 21, company response to clarification). These results are qualitatively similar to those in the overall cohort (Table 31, CS). No longer-term biologic-experienced data were provided for the DLQI outcomes, even though long term data were available for the overall cohort (Figures 15 and 16, CS).

3.5 HS0001 trial

This trial excluded any patients that were biologic-experienced and so details have not been included here. Details of the HS0001 trial are available in Section B 2.6.10.2 of the CS.

3.6 Real-world cohort study

Data have been reported for a French cohort of HS patients.[13] All had received numerous prior antibiotics, and all had received prior biologics, such as adalimumab, infliximab and secukinumab.[13] Patients were given bimekizumab 320 mg every four weeks for four months.

At 12 weeks, 64% (45/72) of patients had HiSCR50 responses, with 42% achieving HiSCR75 and 12% achieving HiSCR90. At week 24, the proportions were: HiSCR50, 72%; HiSCR75, 48%; HiSCR90, 15%. Very limited details of this study were presented in the CS, and the dosing regimen is not the recommended dose (320 mg Q2W for the first 16 weeks); therefore, these results provide only limited evidence for a good HiSCR response amongst patients who have received prior biologics.

3.7 Adverse event and safety data

Adverse event (AE) data were not available for the biologic-experienced subgroup. The EAG has no reason to believe that prior efficacy failure on a biologic would affect the AE profile on a related biologic in the same way that it might affect efficacy, and so the overall cohort safety outcomes are

provided below, in the belief that these will provide a reasonable indication of the adverse event profile in the biologic-experienced population.

3.7.1 Adverse reactions at 16 weeks in BE HEARD trials

Safety outcomes at week 16 are summarised in Tables 47 and 49 of the CS.

While there were no serious treatment-emergent adverse events (TEAEs) in the placebo group, these were experienced by 2.6% of those taking bimekizumab Q2W. The most common TEAEs were hidradenitis (7.6% and 10.3% in the Q2W and placebo groups respectively), coronavirus infection (3.5% and 1.4%), oral candidiasis (7.1% and 0%), diarrhoea (6.3% and 4.8%) and headache (6.9% and 6.8%). TEAEs of interest included infections and infestations (33.5% and 20.5% in the Q2W and placebo groups respectively), hypersensitivity reactions (11.1% and 3.4%), adjudicated suicidal ideation or behaviour (0.2% and 0%), hepatic events (2.4% and 2.7%), and definite or probable adjudicated inflammatory bowel disease (IBD) (0.2% and 0%).

The company clarified that the adverse event of hidradenitis is “a combination of different reported terms, with the most frequently reported terms related to HS abscesses, pain due to HS, and worsening of HS.” The |EAG interprets this as meaning that the adverse event of hidradenitis indicated exacerbations of hidradenitis symptoms.

3.7.2 Adverse reactions at 48 weeks in BE HEARD trials

Tables 48 and 49 of the CS summarise the adverse events occurring up to 48 weeks. Serious TEAEs were experienced by 6.4% of all those receiving bimekizumab at any dose during the trial period (the active medication set). Serious TEAEs included hidradenitis, suicidal ideation, cellulitis, skin pain, skin pain and nephrolithiasis. TEAEs leading to discontinuation were experienced by 6.7% of the bimekizumab recipients. The most common TEAEs were hidradenitis (18.7%), coronavirus infection (10.8%), oral candidiasis (11.2%), diarrhoea (8.5%) and headache (8.6%). In terms of TEAEs of interest, 58.1% experienced infections and infestations, 19% hypersensitivity reactions, 0.5% adjudicated suicidal ideation or behaviour, 0.3% adjudicated major adverse cardiac event, 4.4% hepatic events, and 0.7% definite or probable adjudicated IBD. One death occurred during the trial, but this was due to congestive heart failure and so was unrelated to treatment.

3.7.3 Adverse reactions at 96 weeks in BE HEARD trials

Preliminary data from the open label BE HEARD EXT study were summarised in Table 50 of the CS and did not identify any new safety issues.

3.7.4 Adverse reactions in HS0001 at 12 weeks

The proportion of patients experiencing TEAEs was similar across treatment groups; bimekizumab 70%, adalimumab 71%, placebo 62%. Serious TEAEs were experienced by 2 patients in the bimekizumab group (anaemia and empyema), 1 patient in the adalimumab group (hidradenitis) and 2 patients in the placebo group. Only one discontinuation due to TEAEs occurred, which was in the bimekizumab group.

3.8 Critique of trials identified and included in the indirect comparison and multiple treatment comparisons

The BE HEARD evidence did not cover the decision problem comparison of bimekizumab versus secukinumab, and so indirect treatment comparisons were carried out by the company to compare bimekizumab to secukinumab. An NMA was carried out using the 16-week data from the BE HEARD trials and 12 or 16-week data from comparator trials. As the bimekizumab and secukinumab trials after 16 weeks were not placebo controlled, an unanchored MAIC was necessary to compare bimekizumab at 48 weeks to secukinumab at 52 weeks.

The original NMA and MAIC analyses included patients who were biologic-naïve. This section and those that follow (Section 3.9 and Section 3.10) therefore focus upon the analyses conducted in the more relevant biologic-experienced subgroups, which were available for four trials and obtained during the clarification process. The EAG notes that the full network (including biologic-naïve patients) also included adalimumab trials, but as adalimumab was not considered to be a comparator treatment, those trials are not considered in this report. Details of the overall NMA and MAIC analyses are available in the CS, and also summarised in Appendix 1.

It is likely that the systematic review correctly identified all relevant trials for the NMA and MAIC analyses. The protocol for the systematic review was appropriate, and search strategies appeared satisfactory (see Section 3.1). Methodology for decisions on inclusion and data extraction appeared to be appropriate. Four randomised trials were identified that involved biologic-experienced participants, covering bimekizumab, secukinumab and placebo. Dosages were consistent across trials. Table 12 summarises the studies and the comparisons each study contained.

Table 12 Summary of comparisons in each included randomised trial

Trial	Comparison
BE HEARD I	Bimekizumab 320 mg Q2W vs bimekizumab 320 mg Q4W vs placebo
BE HEARD II	

SUNRISE	Secukinumab 300 mg Q2W vs Secukinumab 300 mg Q4W vs placebo
SUNSHINE	
Q2W, every 2 weeks; Q4W, every 4 weeks.	

A summary of key population characteristics in biologic-experienced patients only is presented in Table 13. Fuller results are given in Table 28 of the company response to clarification. Patient characteristics were similar across trials for most variables, but there appeared to be differences for potential outcome modifiers such as weight, BMI, Hurley stage, DLQI, IHS4 and antibiotic use. Such inconsistency might affect the transitivity assumption in the NMA, but since there were no direct comparisons of secukinumab and bimekizumab in the network it was not possible to formally evaluate inconsistency.

Table 13 Characteristics of BE HEARD I and SUNSHINE/SUNRISE trials (biologic-experienced subgroup)

	BE HEARD I and BE HEARD II		SUNSHINE and SUNRISE		
Category	**Placebo n = 29**	**BKZ Q2W/Q2W and Q2W/Q4W n = 115**	**Placebo n = 94**	**SEC Q2W n = 80**	**SEC Q4W n = 81**
Age, years, mean ± SD	39.5 ± 12.1	38.6 ± 13.3	37.8 ± 11.6	40.3 ± 12.9	38.7 ± 12.1
Female	21 (72.4)	57 (49.6)	57 (60.6)	44 (55.0)	46 (56.8)
Body weight, kg, mean ± SD	94.0 ± 27.0	96.7 ± 26.5	92.2 ± 21.8	95.9 ± 24.5	95.8 ± 23.8
BMI, kg/m^2, mean ± SD	32.69 ± 8.67	32.11 ± 7.95	31.6 ± 6.9	32.5 ± 7.6	32.8 ± 8.2
Duration of disease, years, Mean ± SD	10.96 ± 8.58	8.79 ± 7.79	9.4 ± 7.0	9.5 ± 8.4	9.2 ± 8.4
Hurley stage II, n (%)	11 (37.9)	42 (36.5)	46 (48.9)	33 (41.3)	43 (53.1)
Hurley stage III, n (%)	18 (62.1)	73 (63.5)	47 (50.0)	47 (58.8)	38 (46.9)
AN count, mean ± SD	15.66 ± 8.71	16.62 ± 13.51	15.5 ± 9.8	15.1 ± 11.1	15.7 ± 11.3
DLQI total score, mean ± SD	13.6 ± 8.1	13.0 ± 6.8	15.1 ± 6.9 (n=86)	16.8 ± 6.5 (n=68)	16.4 ± 6.7 (n=71)
Antibiotic use (derived) Yes	3 (10.3)	8 (7.0)	85 (90.4)	66 (82.5)	73 (90.1)
Prior biologic use for HS, n (%) Yes	29 (100)	115 (100)	94 (100)	80 (100)	81 (100)

AN, abscess and inflammatory nodule; BKZ, bimekizumab; BMI, body mass index; DLQI, Dermatology Life Quality Index; HS, hidradenitis suppurativa; kg, kilogram; n, number; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; SEC, secukinumab.

3.9 Network meta-analyses (NMAs)

3.9.1 Methods

The NMA for 0-16 weeks (biologic-experienced patients only) was set up according to the network diagram in Figure 3. Treatments included:

1) placebo (PBO),
2) bimekizumab 320 mg every two weeks and every four weeks (BKZ Q2W and Q4W),
3) secukinumab 300 mg every two weeks and every four weeks (SEC Q2W and Q4W).

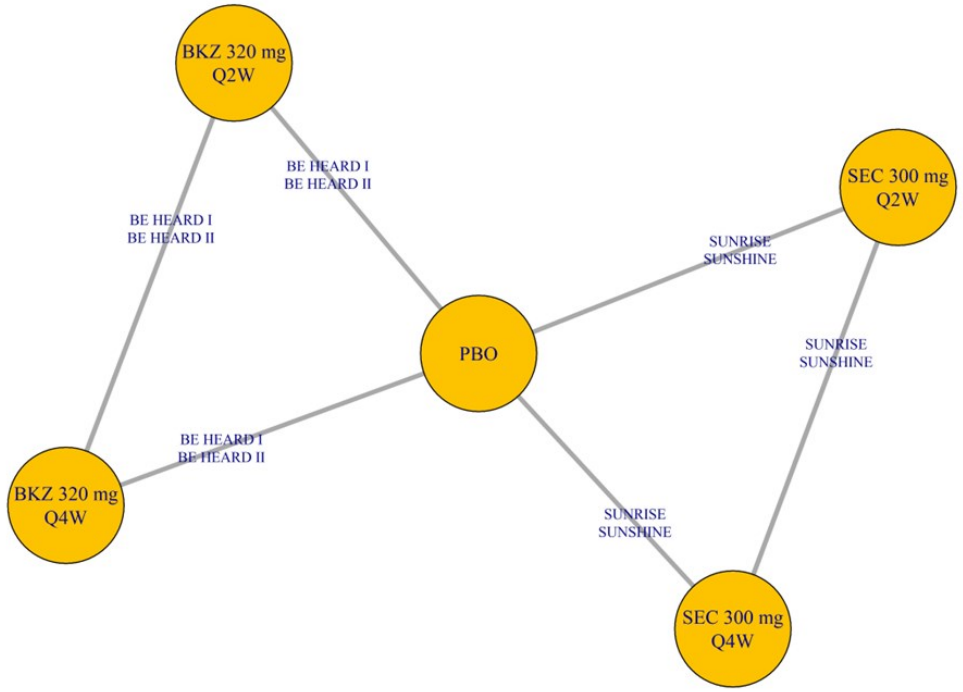
Only the bimekizumab 320 mg every two weeks dose (which combines the data for Q2W/Q4W and Q2W/Q2W groups of BE HEARD I and II) represents the dose used for the first 16 weeks in the decision problem, and so this is the only bimekizumab dose reported here.

A separate NMA was carried out for each of the following outcomes at week 16:

1) HiSCR50, HiSCR75,
2) IHS4-55,
3) percent change in AN count,
4) flare,
5) reduction in worst skin pain (NRS30),
6) DLQI MCID 5-point reduction
7) EQ5D VAS.

No NMAs were presented for IHS4 change or DT count, which had been requested by the EAG during clarification, and the reason given was that outcome data were not available for the biologic-experienced population.

Figure 3 NMA evidence network for biologic-experienced patients at week 16 (Figure 39, CS Appendices)



A Bayesian Markov Chain Monte Carlo approach was conducted in WinBUGS. Fixed effect models were used for all analyses because the Deviation Information Criterion (DIC) in the fixed effect model was no more than 5 points above the random effects model and the networks generally contained a sparse number of trials.

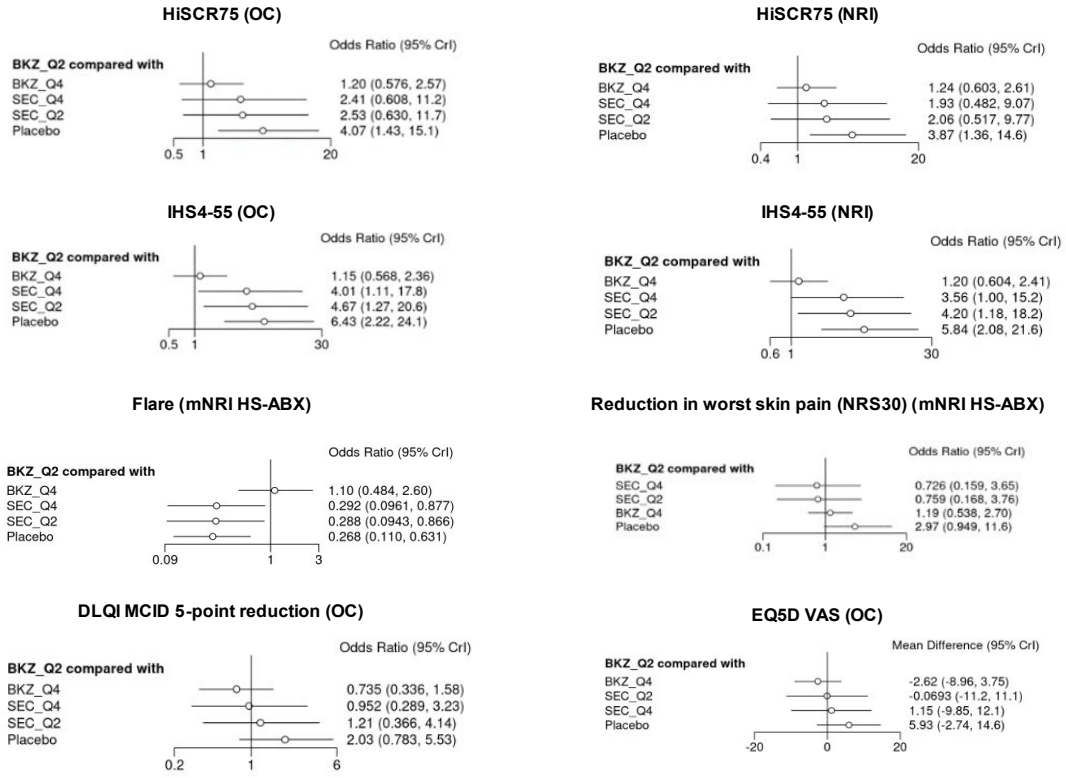
The HiSCR analyses in the predominantly biologic-naïve populations involved a post hoc placebo-adjustment using a meta-regression model in the overall analysis. This appears appropriate, as there was a potentially confounding trend between the magnitude of the placebo effect and the relative effect in the included trials (Figure 40, CS appendix). For other outcomes this adjustment was not used. The EAG agree with the use of a placebo adjustment as there was evidence that they gave a better fit than an unadjusted RE analysis (Table 29, company response to clarification).

Only the HiSCR50, percentage change in AN count, flare and NRS30 outcomes were based on the "HS-ABX" data adjusted for antibiotic use, which will give consistency with the secukinumab trials, that had used an HS-ABX analysis. It is therefore unclear why the other outcomes did not use HS-ABX analysis data.

3.9.2 Clinical findings

Figure 4 summarises the comparisons between bimekizumab, secukinumab and placebo at 16 weeks for all included outcomes, in the biologic-experienced subgroup. The EAG notes that results are broadly consistent across outcomes, with odds of most outcomes being around 3 to 6 times better on bimekizumab than placebo. Bimekizumab may also be superior to secukinumab at reducing disease severity, although this is not always statistically significant due to small sample sizes. Bimekizumab appears similar to secukinumab at reducing pain and for quality of life outcomes. Full details for each outcome are presented in the following sections.

Figure 4 NMA results at 16 weeks for biologic-experienced patients (Figure 4 of clarification response)



3.9.2.1 Clinical response

The NMA analysis restricted to the biologic-experienced subgroup is summarised in Table 14 below. For both response outcomes, there was a significant benefit for bimekizumab Q2W over placebo. The point estimates also indicated a benefit over both doses of secukinumab, but credible intervals were wide due to the small sample sizes.

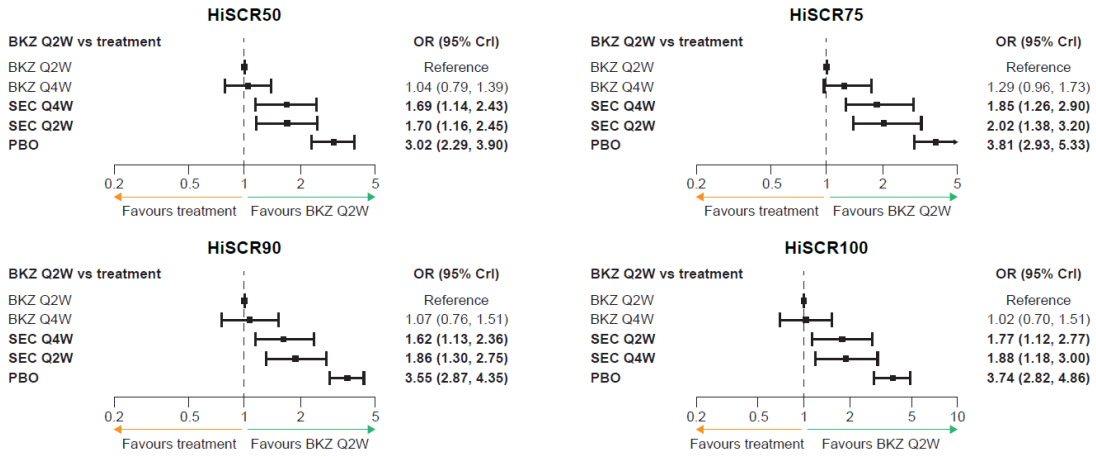
Figure 5 presents the results for the full data analysis, including biologic-naïve patients. These results have similar estimates to those in the analysis of biologic-experienced patients, but with narrower credible intervals due to the larger sample sizes (see also Appendix 1). Hence it appears reasonable to

assume that relative treatment effects are consistent between biologic-experienced and biologic-naïve patients.

Table 14 NMA of clinical response outcomes in the biologic-experienced subgroup

Outcome	Bimekizumab Q2W versus: [OR (95% CrI)]		
	Secukinumab Q2W	Secukinumab Q4W	Placebo
HiSCR50	1.97 (0.67, 6.27)	1.90 (0.65, 6.00)	3.08 (1.31, 8.09)
HiSCR75	2.06 (0.52, 9.77)	1.93 (0.48, 9.07)	3.87 (1.36, 14.60)
CrI, credible interval; HiSCR, Hidradenitis Suppurativa Clinical Response; OR, odds ratio; Q2W, every 2 weeks, Q4W, every 4 weeks.			

Figure 5 Results of NMAs of HiSCR outcomes for the full trial populations (CS Figure 20)



3.9.2.2 Disease severity

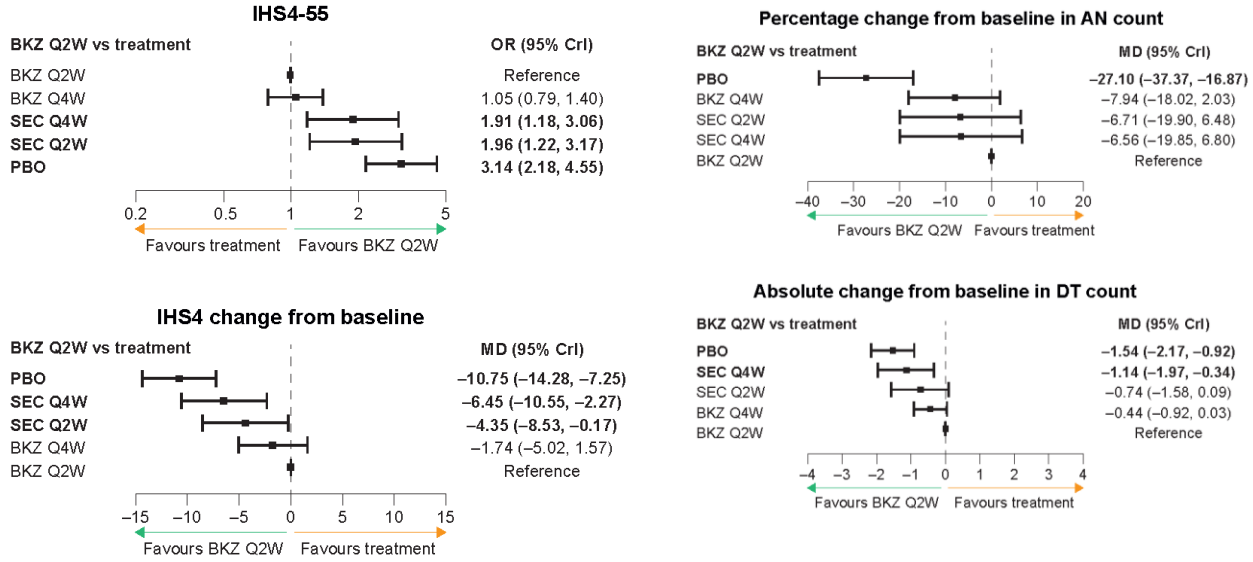
The NMA analysis restricted to the biologic-experienced subgroup is summarised in Table 15 below. For percentage change in AN count, there was a significant benefit over placebo. Compared to both doses of secukinumab, the point estimate suggested a benefit for bimekizumab, but there was a high level of imprecision. For the IHS4-55 outcome there was a significant benefit for bimekizumab over placebo and secukinumab, with higher odds of attaining a 55% reduction in IHS4. The flare outcome demonstrated a significant benefit for bimekizumab over placebo and secukinumab, with lower odds of having a flare.

Figure 6 presents the results for the full data NMA, including biologic-naïve patients. For IHS4-55 and percentage change in AN count, there was some evidence that bimekizumab might be more effective in the biologic-experienced population than in the overall analysis.

Table 15 NMA of disease severity outcomes in the biologic-experienced subgroup

Outcome	Bimekizumab Q2W versus:		
	Secukinumab Q2W	Secukinumab Q4W	Placebo
% change in AN count (lower better) [MD (95% CrI)]	-16.33 (-45.63, 12.62)	-16.45 (-45.52, 12.76)	-39.04 (-60.17, -18.44)
IHS4-55 [OR (95% CrI)]	4.20 (1.18, 18.2)	3.56 (1.00, 15.20)	5.84 (2.08, 21.60)
Flare [OR (95% CrI)]	0.29 (0.09, 0.87)	0.29 (0.10, 0.88)	0.27 (0.11, 0.63)
AN, abscess and inflammatory nodule; CrI, credible interval; IHS4-55, 55% reduction in International Hidradenitis Suppurativa Severity Score System total score; OR, odds ratio; Q2W, every 2 weeks, Q4W, every 4 weeks; WMD, weighted mean difference.			

Figure 6 Results of NMAs of disease severity outcomes for the full trial populations (CS Figures 22 and 23)



3.9.2.3 Discomfort and pain

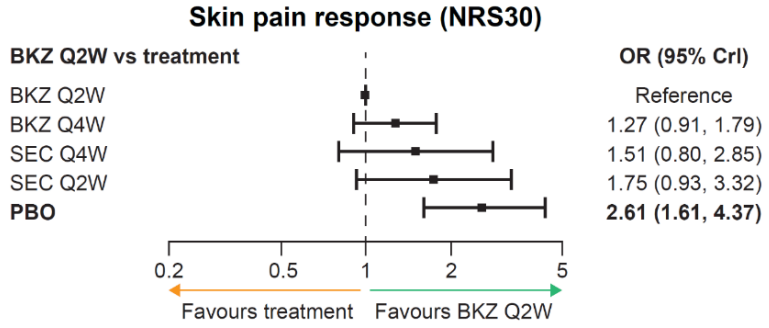
The NMA analysis for reduction in worst skin pain, restricted to the biologic-experienced subgroup, is summarised in Table 16 below. The point estimate indicated a benefit for bimekizumab over placebo, but also a benefit for secukinumab over bimekizumab. However, the credible intervals were wide for all analyses, indicating high levels of uncertainty/imprecision.

Figure 7 presents the results for the full data NMA, including biologic-naïve patients. The full-cohort result demonstrated a significant benefit for bimekizumab over placebo. However, for bimekizumab versus secukinumab, the overall results differ from those in the biologic-experienced analysis, with the point estimates indicating a benefit for bimekizumab, although again there were high levels of uncertainty (Appendix 1).

Table 16 NMA of discomfort and pain outcomes in the biologic-experienced subgroup

Outcome	Bimekizumab Q2W versus: [OR (95% CrI)]		
	Secukinumab Q2W	Secukinumab Q4W	Placebo
Reduction in worst skin pain (NRS30)	0.76 (0.17, 3.76)	0.73 (0.16, 3.65)	2.97 (0.95, 11.55)
CrI, credible interval; NRS30, ≥30% reduction and reduction of ≥2 units from baseline in HSSDD weekly worst skin pain numerical rating scale score, assessed in patients with a baseline numerical rating scale score of ≥3; OR, odds ratio; Q2W, every 2 weeks; Q4W, every 4 weeks.			

Figure 7 Results of NMAs of skin pain response for the full trial populations (CS Figure 26)



3.9.2.4 Quality of life

The NMA analysis restricted to the biologic-experienced subgroup is summarised in Table 17. Neither outcome, both of which used potentially biased observed case data, demonstrated a significant benefit for bimekizumab over placebo or secukinumab. Neither of these outcomes were analysed in the overall cohort.

Table 17 NMA estimates of quality of life outcomes for bimekizumab Q2W versus secukinumab Q2W and Q4W in the biologic-experienced subgroup (OC)

Outcome	Bimekizumab Q2W versus:		
	Secukinumab Q2W	Secukinumab Q4W	Placebo
DLQI MCID 5-point reduction [OR (95% CrI)]	1.21 (0.37, 4.14)	0.95 (0.29, 3.23)	2.03 (0.78, 5.53)
EQ5D VAS [MD (95% CrI)]	-0.07 (-11.17, 11.07)	1.15 (-9.85, 12.06)	5.93 (-2.74, 14.57)
CrI, credible interval; DLQI MCID, Dermatology Life Quality Index minimal clinically important difference; EQ5D VAS, 5-dimension EuroQol questionnaire visual analogue scale; Q2W every 2 weeks; Q4W, every 4 weeks.			

3.10 Matched Adjusted Indirect Comparisons (MAIC)

3.10.1 Methods

For the follow-up time of 48 weeks the CS presented a Matched Adjusted Indirect Comparison (MAIC) analysis to compare bimekizumab to secukinumab. This was justified because all patients

allocated to placebo had transferred to active therapy after 16 weeks, so an NMA was not feasible. In the MAIC the data from the Q2W/Q4W arms of the two BE HEARD trials were pooled together and compared to both the 2-weekly (Q2W 300 mg) and 4-weekly (Q4W 300 mg) arms of the SUNSHINE and SUNRISE trials of secukinumab at week 52 (for details of these see Section 3.8).

The EAG notes that the MAICs were performed using the full trial populations, and were not restricted to the relevant biologic-experienced population of patients who had previously received, or were contraindicated to, adalimumab.

The MAIC was adjusted for sex, race, age, BMI, duration of HS, smoking, severity (Hurley stage III), location, DT count, abscess and inflammatory nodules count, prior biologics and concomitant antibiotics. It was not adjusted for components of the abscess and inflammatory nodules count, due to the collinearity between these variables and the combined AN count, or for DLQI, on the grounds that doing so led to a small effective sample size. Patients in BE HEARD who received antibiotics were treated as non-responders to treatment only if antibiotics were given as a rescue treatment. This was in line with the analysis performed in the trials of secukinumab.

Only limited details on the methods used for the MAIC analyses were presented, so the EAG cannot fully critique the approach used. However, it appears to be a suitably conducted MAIC analysis. The choice of trials and trial arms was appropriate, and the EAG agrees that it is reasonable to only compare bimekizumab to secukinumab at 48 and 52 weeks.

A suitable range of prognostic factors were used for adjustment, that are likely to represent the main factors which might influence treatment effectiveness. The exclusion of DLQI from adjustment might lead to bias, because there was some evidence of differences in DLQI scores between the trials (see Table 13). The EAG does not have access to the data required to assess whether this led to actual bias. As with any MAIC, the possibility that important prognostic factors were missed that could bias the results cannot be ruled out.

3.10.2 Clinical findings

Details of the adjustments performed in the MAIC analyses were presented in CS Appendix D.1.6.2 Tables 112 and 113. BE HEARD I/II and SUNRISE/SUNSHINE were broadly similar in characteristics before adjustment, but symptoms were generally slightly more severe in the BE HEARD trials (e.g. longer HS duration, more DTs and abscesses, more at Hurley stage III).

The effective sample size for bimekizumab arms after matching was 226 for comparison with secukinumab Q2W and 208 for comparison with the secukinumab Q4W group (compared to an original total of 292). So, the effective sample size is sufficiently large for analyses to be expected to be robust.

After adjustment, all factors were identical in both trials to two decimal places (see CS Appendix Tables 112 and 113). The EAG considers it highly implausible that perfect matching can be achieved in a MAIC across 12 factors and both secukinumab arms. The EAG therefore considers that either the supplied tables are incorrect, or that the matching was not performed correctly. The EAG requested clarification on this, but did not receive a satisfactory answer. Consequently, the EAG considers that the MAIC may have been performed incorrectly, and its results may not be reliable.

3.10.2.1 HiSCR outcomes

Table 18 summarises the results of the MAICs comparing bimekizumab (Q2W/Q4W) with secukinumab for HiSCR outcomes (taken from CS Figure 27). These results suggest that bimekizumab doubles the odds of successful response to treatment (based on HiSCR score), with results being statistically significant for all analyses and consistent across secukinumab doses and levels of HiSCR.

The EAG notes that these are analyses of all patients, and are not restricted to biologic-experienced patients. Consequently, they may not represent the results in the relevant population of patients who have previously received, or are contraindicated for, adalimumab. By comparison with the equivalent results from the NMAs at 16 weeks (see Section 3.9.2.1), the EAG expects that the odds ratios for biologic-experienced patients only may be similar to those for all patients, but the confidence intervals would be much wider, and plausibly not statistically significant.

Table 18 Results of MAICs for HiSCR outcomes

HiSCR outcome	**Odds ratio (95% CI) when bimekizumab is compared to:**	
	Secukinumab 300 mg Q2W	**Secukinumab 300 mg Q4W**
HiSCR50	2.00 (1.42 to 2.80)	2.06 (1.45 to 2.92)
HiSCR75	1.91 (1.35 to 2.70)	2.13 (1.49 to 3.05)
HiSCR90	2.05 (1.39 to 3.04)	2.04 (1.36 to 3.04)
CI, confidence interval; HiSCR, Hidradenitis Suppurativa Clinical Response; Q2W, every 2 weeks; Q4W, every 4 weeks.		

3.10.2.2 Other outcomes

MAICs were not performed for any outcomes other than HiSCR.

3.11 Additional work on clinical effectiveness undertaken by the EAG

The EAG have not performed any further analyses of the trial data, or any further indirect treatment comparisons.

3.12 Conclusions of the clinical effectiveness section

The evidence supplied by the company for bimekizumab as a treatment for moderate to severe HS is drawn largely from two trials (BE HEARD I and BE HEARD II). These trials did not match the proposed positioning of bimekizumab, which is that it should be offered to patients for whom adalimumab had been ineffective (i.e. they are biologic-experienced), or for whom adalimumab is unsuitable or contraindicated. Most patients in the trials had no prior exposure to adalimumab (they were biologic-naïve); only 17.3% had prior exposure to adalimumab and a small number had exposure to prior biologic therapies other than adalimumab. The trials also included bimekizumab arms that did not use the recommended dose (which is 320 mg every 2 weeks for 16 weeks, and every 4 weeks thereafter).

The EAG therefore preferred to focus on the subgroups within the trials most relevant to this assessment, namely biologic-experienced patients receiving the recommended dose (or placebo). This subpopulation was substantially smaller than the overall trial (just 115 patients on bimekizumab; 29 on placebo). Consequently, the EAG considers that the evidence base for bimekizumab is much smaller than is suggested by the CS.

The evidence from the BE HEARD trials at 16 weeks indicates that bimekizumab was superior to placebo in biologic-experienced patients for the primary HiSCR outcomes. For example, 52.7% of patients on bimekizumab achieved HiSCR50 (50% or greater reduction in AN count), compared to only 27.6% on placebo. The EAG notes that the absolute values of HiSCR50 response in the biologic-experienced population were smaller than for the overall trial population, including biologic-naïve patients (56.8% of patients achieved HiSCR50 in the overall trial bimekizumab Q2W/Q4W and Q2W/Q2W population, but only 52.7%% of patients achieved HiSCR50 in the biologic-experienced bimekizumab Q2W/Q4W and Q2W/Q2W population). This suggests that bimekizumab might be slightly less effective, in absolute terms, if patients have previously received adalimumab.

Results for other outcomes also suggested that bimekizumab was superior to placebo in biologic-experienced patients at 16 weeks, including disease severity, discomfort and pain, and quality of life outcomes.

Beyond 16 weeks all patients on placebo transferred to receiving bimekizumab, so no direct comparative or blinded data exists. Data at 48 weeks for the biologic-experienced subgroup suggested that levels of HiSCR response were maintained between 16 and 48 weeks. This differed from the overall trial results, where there was some evidence of continued improvement after 16 weeks.

Bimekizumab was compared to placebo and secukinumab at 16 weeks using network meta-analyses (NMAs). The NMAs suggested a clear superiority of bimekizumab over placebo in biologic-

experienced patients for most outcomes. For example, the odds of achieving HiSCR50 were 3.08 times higher on bimekizumab than placebo (95% CrI 1.31 to 8.09). The NMAs also suggested superiority of bimekizumab over secukinumab for most outcomes except quality of life outcomes, but this was less conclusive. For example, the odds of achieving HiSCR50 were 1.97 times higher on bimekizumab than secukinumab Q2W (95% CrI 0.67 to 6.27). As the NMAs were essentially a comparison of the BE HEARD trials of bimekizumab with the SUNSHINE and SUNRISE trials of secukinumab they could be biased if there are structural differences between the trials. The EAG also notes the very small sample sizes when analysing only the biologic-experienced subgroups.

Bimekizumab was compared to secukinumab at 48 weeks using matched adjusted indirect comparisons (MAICs) because there were no patients receiving placebo beyond 16 weeks. The results suggested that the possible benefits of bimekizumab over secukinumab observed at 16 weeks are retained at 48 weeks. For example, the odds of achieving HiSCR50 were 2 times higher on bimekizumab than secukinumab Q2W (95% CI 1.42 to 2.80). The EAG has concerns that the MAICs may not have been adjusted correctly because the adjusted data were implausibly similar across trials. MAICs were also not available for just the biologic-experienced patients. The EAG therefore advises caution when interpreting the MAIC analyses.

Adverse event data were not available for the biologic-experienced subgroup. However, the EAG has no reason to believe that prior efficacy failure on a biologic would affect the adverse event profile of bimekizumab. The majority of patients in each treatment arm (bimekizumab every 2 weeks, bimekizumab every 4 weeks and placebo) experienced a TEAE up to week 16. However, the proportion of patients who experienced a severe or serious TEAE up to week 16 was low and only a few patients discontinued treatment because of TEAEs. By week 48 the proportion of patients experiencing a TEAE, severe TEAE or serious TEAE had increased, although the exposure-adjusted incidence rate remained relatively low.

The EAG concludes that there is good evidence overall to demonstrate that bimekizumab is superior to placebo after 16 weeks for all key outcomes, including HiSCR, in the “biologic-experienced” population of interest. There is also good, but non-comparative, evidence to suggest that the effect of bimekizumab is maintained for at least 48 weeks. The EAG suggests that the results in the “biologic-experienced” subgroup are most relevant to the decision problem, and should be preferred over the overall trial results when assessing the clinical value of bimekizumab. There is also some evidence that bimekizumab is superior to secukinumab up to 48 weeks. However, as the size of the “biologic-experienced” subgroup was small, and because the comparison is indirect only, the EAG suggests this conclusion should be treated with caution, and that the exact size of the benefit of bimekizumab over secukinumab is uncertain.

3.12.1 Remaining areas of uncertainty

The EAG notes the following areas of remaining uncertainty in the clinical evidence:

1. The number of patients who were biologic-experienced, and so of most relevance to this appraisal, was small. Consequently, the evidence base is much smaller, and estimates of effect for bimekizumab are considerably less certain, than is suggested in the CS.
2. Only one of the dose arms used in the BE HEARD trials was the recommend dose (320 mg Q2W/Q4W). Therefore, the evidence base at the recommended dose is small.
3. Absolute effects for many outcomes, including HiSCR, in the biologic-experienced subgroup (particularly at the recommended 320 mg Q2W/Q4W dose) were not as good as in the overall cohort of patients across all doses. Therefore, outcomes in clinical practice are unlikely to be as good as observed in the BE HEARD trials overall.
4. The BE HEARD trials were only placebo controlled for the first 16 weeks (i.e., before the maintenance dose of 320 mg every four weeks). All longer-term evidence is therefore non-comparative and indirect, so may be subject to bias.
5. Evidence comparing bimekizumab to secukinumab is entirely indirect, effectively drawn from only one trial of each treatment (BE HEARD I/II vs SUNSHINE/SUNRISE), and the sample size for "biologic-experienced" patients was small. Consequently, there is considerable uncertainly around the validity and accuracy of results when comparing bimekizumab to secukinumab.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company undertook three systematic literature reviews to identify relevant economic evaluations, health-related quality of life (HRQoL), and cost and healthcare resource use measurement and valuation studies for patients with HS. These searches were conducted to 6 November 2023.

The methods and findings of the literature reviews conducted by the company were described briefly in the CS and in full in Appendix G for cost-effectiveness studies, Appendix H for HRQoL studies, and Appendix I for cost and healthcare resource use measurement and valuation studies.

4.1.1 Search strategy

Appendix G of the CS included the update searches carried out in November 2023 to identify studies on the cost-effectiveness of interventions for HS. The original searches carried out in May 2023 were provided within the company response to the EAG's clarification questions (CQs) in a report by IQVIA.[18]

The EAG found that the searches for cost-effectiveness studies reported in Appendix G and those in the report by IQVIA were high quality and appropriate. A couple of minor weaknesses were noted: the searches were limited to English language studies only and the supplementary search of health technology assessment (HTA) agency websites was fairly limited (NICE and the Scottish Medicines Consortium [SMC] websites only). The search strategy used to search the International HTA database was not reported so could not be appraised by the EAG.

The EAG found that the searches undertaken to identify HRQoL evidence (reported in Appendix H and the company clarification response) were not as comprehensive as expected. Some of the terms for HRQoL were omitted from the strategies used to search MEDLINE and Embase, and supplementary searching was limited to conference abstract searching and ClinicalTrials.gov. These issues may have led to missing HRQoL studies.

The EAG were satisfied that the search strategies used were sufficient to identify existing cost-effectiveness, and cost and healthcare resource use studies. As discussed in later sections, the EAG considered the most appropriate source of HRQoL data to be the BE HEARD studies. The potential omission of HRQoL studies is not therefore a key source of uncertainty.

Table 19 EAG appraisal of evidence identification for review of cost effectiveness and healthcare resource use

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	YES	Search strategies for the original May 2023 searches were missing from the company submission but provided in the company response to the CQs, with the exception of the search strategy used to search the International HTA (INAHTA) database.
Were appropriate sources searched?	YES	The sources searched were appropriate for identifying both unpublished and published economic evaluations, cost studies and resource use studies. Appropriate supplementary searching was undertaken, consisting of the hand searching of 6 relevant conferences, 2 HTA agency websites (NICE and Scottish Medicines Consortium), a search of the INAHTA database, and reference checking of included economic evaluations. A search of further HTA agency websites could have been useful.
Was the timespan of the searches appropriate?	YES	Main databases - 2012 to November 2023. In Embase the search for conference abstracts was limited to more recent conferences taking place during 2021-2023, which is reasonable. Hand search of conference abstracts - 2021-2023. Websites of HTA agencies and the INAHTA database were searched from inception to November 2023.
Were appropriate parts of the PICOS included in the search strategies?	YES	*Population* (HS) AND *Study design* (economic evaluations OR cost studies OR resource use studies).
Were appropriate search terms used?	YES	Search terms (both text word and subject headings) for the population and study design were appropriate and comprehensive in most databases and resources searched. A couple of less used synonyms for HS were missing from the database search strategies – apocrinitis and apocrine acne.
Were any search restrictions applied appropriate?	NO	Limit to English language studies applied to the databases searches, therefore language bias is possible.
Were any search filters used validated and referenced?	NO	A very comprehensive set of search terms (both text word and subject headings) for economic evaluations, economic models, cost studies and resource use studies were included in the search strategies for MEDLINE and Embase. The EAG therefore has no concerns that validated search filters were not used.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

4.1.2 Inclusion/exclusion criteria

For all three reviews, the company included studies based on a population of patients with HS of any severity. Studies were restricted to 2012 onwards for the cost-effectiveness and healthcare resource utilisation reviews, and 2010 onwards for the HRQoL review. The HRQoL review also excluded

studies which did not involve at least 100 patients. No geographical restrictions were placed on the studies.

Two reviewers reviewed all abstracts according to the eligibility criteria which then underwent full text screening. A third reviewer reviewed any studies that were queried at either selection stage.

The EAG considered the eligibility criteria and the company's assessment of identified studies against them to be generally appropriate.

4.1.3 Identified studies

The review of cost-effectiveness studies identified five published economic evaluations, all conducted from a UK perspective. These included the NICE appraisals for adalimumab (TA392) [4] and secukinumab (TA935),[5] the SMC evaluation of adalimumab[19] and an early modelling study based on adalimumab.[20] The final publication was an EAG group perspective of the adalimumab NICE appraisal.[21]

In the review of HRQoL studies, 114 studies were included in the final review, of which 17 related to HRQoL data generated with generic instruments. In the final review of HCRU studies, 33 relevant studies were identified of which only two related to patients with HS in the UK.

4.1.4 Interpretation of the review

The EAG considered the methods of the company's literature review sufficient to identify any existing cost-effectiveness analyses conducted in a relevant population and setting. The EAG is satisfied that the model presented by the company represents the most relevant analysis for decision making.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 20 summarises the EAG's assessment of whether the company's economic evaluation meets the NICE reference case and other methodological recommendations.

Table 20 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	**Yes.** QALY benefits for treated patients were considered through health state utility values. Health benefits on BSC based on assumptions which may not

		appropriately represent NHS outcomes.
Perspective on costs	NHS and PSS	**Yes.** An NHS and PSS perspective on costs was considered.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	**Yes.** A cost-utility analysis was implemented with an incremental analysis performed.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	**Partly.** The economic model adopted a lifetime (60-year) time horizon. A 70-year time horizon may be more appropriate given the young starting age of the cohort.
Synthesis of evidence on health effects	Based on systematic review	**Partly.** The company performed a systematic review to identify relevant data sources. The company undertook an NMA of available trial evidence. Transition probabilities for active treatment were not fully propagated through the model, underestimating long-term outcomes on treatment.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	**Yes.** Health effects were expressed in QALYs. EQ-5D-3L data from BE HEARD I and II was used to inform modelled health state utilities.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	**Yes.** Reported directly from patients with HS based on participant responses from the BE HEARD trials.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	**Yes.** Valued using UK general population tariffs.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	**Yes.**
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	**Yes.** Costs based on UK sources such as NHS reference costs.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	**Yes.** Costs and benefits were discounted at 3.5% per annum.
BSC, best supportive care; EAG, External Assessment Group; EQ-5D, standardised instrument for use as a measure of health outcome; HS, hidradenitis suppurativa; MAIC, matching-adjusted indirect comparison; NHS, National Health Service; NMA, network meta-analysis; PSS, personal social services; QALYs, quality-adjusted life years.		

4.2.2 Model structure

The company developed a *de novo* Markov decision analytic model in Microsoft Excel to assess the cost-effectiveness of bimekizumab versus both secukinumab and best supportive care (BSC) for

adults with moderate-to-severe HS for whom adalimumab is contraindicated or otherwise unsuitable. Patients in the bimekizumab and secukinumab arms who discontinued the primary treatment were modelled to switch to BSC and were subject to transition probabilities and costs equivalent to the BSC comparator arm beyond this point. In the company's base case, switching to BSC restricts the transitions possible in any given cycle, and these patients exist in what essentially comprises a separate model structure (discussed further below).

The base-case model structure consists of six mutually exclusive health states based on five categories of HiSCR response, and an absorbing death state. All patients enter the model in the non-response health state, and all are treated with the primary intervention for four model cycles (i.e. the initial treatment phase). Treatment response is assessed at Week 16 (model cycle 4). Achieving a partial response (HiSCR25 or above) at this time point is necessary to continue on treatment with the primary intervention. Beyond this point, the transition probabilities applied are based on 'maintenance phase' treatment. Lower HiSCR categories indicate more severe disease and are associated with a poorer quality of life and additional management costs. The modelled health states are as follows -

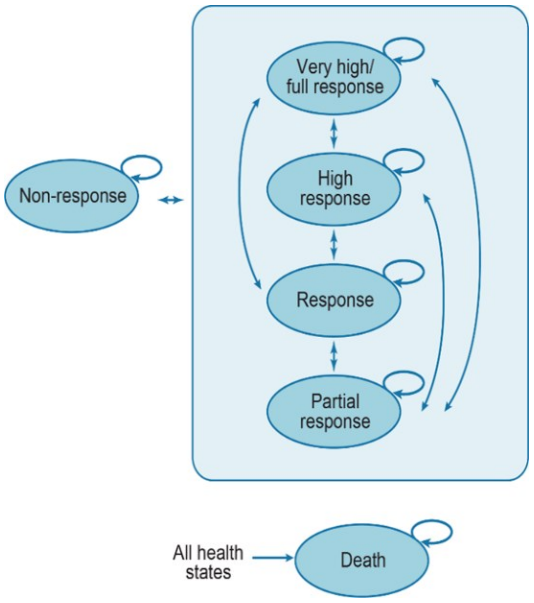
- "Non-response" (HiSCR<25), corresponding to a less than 25% reduction in total AN count and/or an increase in abscesses or draining tunnels;
- "Partial response" (HiSCR25), a reduction in total AN count of 25% and less than 50% and no increase in abscesses or draining tunnels;
- "Response" (HiSCR50), a reduction of 50% and less than 75% and no increase in abscesses or draining tunnels;
- "High response" (HiSCR75), a reduction of 75% and less than 90% and no increase in abscesses or draining tunnels;
- "Very high response" (HiSCR90), showing an AN count reduction from baseline of 90-100% and no increase in abscesses or draining tunnels;
- "Death", absorbing health state.

The cohort was assumed to enter the model in the "non-response" health state. At the end of the first cycle, patients could transition to a response state (HiSCR 25, 50, 75, 90) or could remain in the non-response state. Transitions in subsequent cycles could see patients improve their response (moving to a higher response level), deteriorate (drop one or more response levels), or maintain their current response level. The "death" health state was absorbing and transitions to this state were possible from any other state. The transition probabilities applied in a given cycle depended on the model phase, that is, the initial- or maintenance- treatment phase. For the active treatment arms (bimekizumab and secukinumab), transition probabilities varied according to the initial treatment phase (up to Week 16) and the maintenance phase (post-16 weeks). The BSC arm has a third, 'long-term' treatment phase,

comprising the remainder of the modelled time horizon beyond Week 48, during which time alternative efficacy assumptions are applied. This is discussed further in Section 4.2.6.

All possible transitions are depicted in the company's model schematic, reproduced in Figure 8. In the executable model, these transition possibilities only apply to patients on BSC during the induction phase. Implicit in the transitions applied to the BSC arm is the assumption that patients cannot improve following their response level between Week 16 and Week 48, and can only remain in their current health state, or move to a lower response category. After Week 48 of the modelled time horizon, the company assume that patients on BSC maintain their 48-week response level indefinitely.

Figure 8 Company's base-case model schematic (CS Figure 29, Page 129)



All responder states were subject to general population mortality rates (HiSCR≥25). A standardised mortality ratio (SMR) was applied to general population mortality rates, reflective of an increased risk of mortality for patients in the "non-response" state. The mortality parameters applied in the model are discussed in Section 4.2.6.3.

The company described how discontinuation from active treatments was allowed in the model due to three explicit stopping rules. All three reasons for discontinuation had the same consequences for patients, regardless of whether they were primary non-responders (lack of efficacy at Week 16), secondary non-responders (loss of response beyond Week 16) or discontinued due to other reasons such as adverse events. All discontinuing patients immediately switched to BSC costs and outcomes until the end of the model time horizon. Upon discontinuing, patients pass through a series of tunnel states in which transition probabilities are based on the initial treatment period data for placebo,

before Week 16-48 BSC transition probabilities are applied, then beyond Week 48, the 'long-term' efficacy assumption applies. Discontinuation is discussed further in Section 4.2.6.2.

Points for critique

The EAG considered the company's general approach to the model structure to be broadly appropriate and consistent with the approaches taken in the appraisals of secukinumab (TA935) and adalimumab (TA392). The company's model departed slightly from these appraisals due to the addition of a "very high response" state to represent patients who achieve HiSCR≥90. By contrast, the other appraisals represented the highest response level with a HiSCR75+ state. Clinical advice provided to the EAG suggested that the HiSCR90 response level would be clinically meaningful to patients who achieve it relative to a HiSCR75 response. The EAG consider the inclusion of this outcome to be an appropriate way of capturing the additional potential benefits of bimekizumab relative to secukinumab.

The EAG had significant concerns regarding the implementation of the stopping rule for secondary loss of response in the model. As discussed in Sections 4.2.4, 4.2.6.2, and 4.2.8.1, the stopping rule for secondary non-response was developed in response to extensive clinical feedback during TA935, where it was established that active treatment should only be discontinued when a patient stops responding during the maintenance phase and maintains non-response for 12 weeks, typically following the addition of other treatments and/or surgery with the aim of re-establishing a response. As the present model structure does not allow patients to regain response whilst remaining on active treatment according to the transition probabilities based on the BE HEARD studies and NMA, it fails to capture a potentially substantial component of the treatment effect associated with bimekizumab and secukinumab, and likewise fails to represent observed outcomes on maintenance treatment in the trials.

Furthermore, the structure results in a significant underestimate of treatment costs, as all patients who discontinue beyond Week 16 may be expected to remain on treatment for at least a further 12 weeks before discontinuing or re-establishing a response to treatment. Significant changes to the model structure would be required to implement this 12-week stopping rule in the form of a series of tunnel states whereby only when a patient has maintained a lack of response for 3 consecutive cycles, would they discontinue from an active treatment. The EAG requested that the model be amended for consistency with the accepted model structure in TA935, but this analysis was not provided by the company in their clarification response. The EAG note that this assumption may be challenging to implement in full due to limits on the number of tunnel states that could reasonably be used. The effect of failing to properly model discontinuation in secondary non-responders is that discontinuation from active treatment is overestimated, and thus QALY-gain and treatment costs will be potentially significantly underestimated. This issue is described in more detail in Sections 4.2.4, 4.2.6.2, and 4.2.8.1.

The EAG were also concerned that the structural assumptions imposed on BSC transitions – both as a comparator treatment and treatment subsequent to discontinuation of bimekizumab or secukinumab – artificially inflate the apparent effectiveness of the active treatment options. As is discussed further in Section 4.2.6, transitions to higher levels of response were not possible for any patients on BSC between Week 16 and Week 48 in the model base case. This resulted in a proportion of BSC patients with a HiSCR50 response at Week 36 of [redacted] in the model, compared to [redacted] in PIONEER II (which likely underrepresents placebo response), and [redacted] predicted using the NMA to adjust bimekizumab transition probabilities. Beyond Week 48 of the model, patients on BSC remained in their current health state for the remainder of the modelled time horizon. The structure of the company's base-case model may significantly underestimate QALY gain on BSC.

An important consequence of the assumption that BSC patients remain in their Week 48 health state indefinitely is that those who discontinue active treatment for 'other reasons', e.g. due to adverse events, will retain whatever level of response they have achieved indefinitely, either from the point they reach Week 48 of the model time horizon, or immediately following 12 weeks of BSC initial treatment transition probabilities if discontinuation occurs beyond Week 48. This awards the benefits of active treatment indefinitely to discontinuing patients, whilst incurring none of the costs associated with active treatment. Furthermore, patients who discontinue active treatment move into tunnel states which apply initial period transition probabilities for BSC. Patients who regain a response to BSC (i.e. placebo response outcomes) can likewise maintain these outcomes indefinitely. The value case for bimekizumab in the company's submitted model appears to be based around this mechanism of treatment benefit, and incentivises immediate discontinuation and a high response rate for BSC during the initial period, followed by poorer outcomes in the maintenance phase, which are not experienced by those on bimekizumab. This assumption as modelled clearly does not appropriately represent clinical practice, but alone is responsible for ~75% of incremental QALYs attributed to bimekizumab compared with secukinumab and BSC.

The EAG highlighted this issue at the clarification stage and requested that if the 'durable response' assumption were to be included in the model, that transition probabilities on BSC beyond Week 48 be applied only once a patient who has discontinued bimekizumab or secukinumab has been on BSC for 48 weeks, rather than from Week 48 of the model time horizon (CQ B17.2). However, the company stated this was not possible in the time available given the complexity of the necessary structural changes. Scenarios which applied alternative assumptions around the long-term efficacy of BSC were provided and are discussed further in Section 4.2.6. The EAG explore scenarios in Section 6 which allow BSC patients to transition freely between health states indefinitely.

4.2.3 Population

The characteristics of the modelled population are based upon the BE HEARD I and II trial populations (n = 1,014), and considered patients aged 18 or over who had a diagnosis of moderate-to-severe HS. The baseline characteristics of the modelled population are presented in Table 21. The probabilistic analysis presented by the company included no sampling of baseline characteristics.

Table 21 Baseline characteristics of modelled population

Parameter	Mean (SD)	Source
Age	36.6 (12.20)	BE HEARD I & BE HEARD II
Weight (kg)	97.3 (24.38)	
Female (%)	57%	

The model does not distinguish between biologic-naïve and -experienced patients, including data from the whole population of the BE HEARD I and II studies, regardless of prior biologic exposure. These trials included only 191 biologic-experienced patients (18.8%).

Points for critique

The committee in TA935 had concerns relating to the generalisability of the SUNNY trial populations to the NHS with regards to prior biologic exposure. However, on balance they concluded the full population was generalisable to that considered in the decision problem. The NHS population at this position is likely to predominantly comprise patients with previous exposure to adalimumab, but these patients make up only 18.8% of the trial population in the BE HEARD studies. Whilst adalimumab and bimekizumab have different mechanisms of action, the effectiveness of bimekizumab appeared consistently (but not statistically significantly) poorer in the biologic-experienced group compared to the predominantly biologic-naïve population. As discussed in Section 4.2.6, this may over-estimate the effectiveness of treatment with bimekizumab in an NHS setting. The EAG requested that the company present cost-effectiveness results by subgroup according to prior biologic exposure, which are presented in Section 5.3.

4.2.4 Interventions and comparators

The modelled intervention is bimekizumab 320 mg Q2W up to Week 16 followed by 320 mg Q4W maintenance treatment. This is in alignment with the EMA marketing

authorisation granted on 22nd April 2024. Patients who discontinue treatment with bimekizumab at any time go on to receive BSC, the modelled composition of which is described below.

During the initial period, bimekizumab is administered a total of eight times (i.e. every two weeks from Week 0 to Week 16). Patients who achieved at least a partial response (>HiSCR25) at Week 16

are modelled to continue to receive 320 mg of bimekizumab every four weeks, while the remainder discontinue treatment. Maintenance treatment with bimekizumab is modelled to continue until a patient loses response, at which point they switch to BSC. Discontinuation due to AEs was considered separately in the model.

As discussed in Section 2.2.5, following failure on- or contraindication to- adalimumab, current treatment options are secukinumab or BSC. Treatment with secukinumab comprises a loading phase, with 300 mg of secukinumab administered at Weeks 0, 1, 2, 3, and 4, followed by 300 mg every four weeks. This is in alignment with the posology for secukinumab recommended in TA935. The company interpreted the 'monthly' maintenance dosing of secukinumab in the SmPC as every 4.3482 weeks, rather than as Q4W per TA935 in the executable model. The EAG considered this a modelling error, which is corrected in Section 6. If patients were not responding at Week 16, they were assumed to discontinue treatment and switch to BSC. The marketing authorisation for secukinumab allows for the standard Q4W maintenance dose to be increased to Q2W for an additional 12 weeks in patients who do not achieve a response at Week 16, or who have a body weight of 90 kg or higher. In TA935, the committee considered there to be insufficient evidence on the efficacy of this treatment strategy to make specific recommendations on its use but noted that clinicians may apply up-titration in NHS practice as permitted in the licence. The company provided a scenario analysis in their clarification response which implemented an approximation of up-titration for secukinumab, but this was based on a 36-week extension of Q2W treatment to Week 48, rather than Week 28 as preferred by the company in TA935. A model inclusive of the functionality for this scenario was not provided to the EAG in sufficient time to be validated or corrected. The effectiveness and cost-effectiveness of up-titration of secukinumab remains a key uncertainty. The submission also described a stopping rule for secukinumab based on a patient remained in the non-response health state for three consecutive model cycles, after which they would switch to BSC. However, the model included no such stopping rule and the company stated that this description was included in error. Discontinuation due to AEs was considered separately in the model.

Best supportive care was modelled as both a direct comparator for bimekizumab, and as a subsequent therapy following discontinuation of bimekizumab or secukinumab. The composition of BSC was based partially upon clinical advice received by the manufacturer of secukinumab, considered in TA935. BSC primarily comprised topical antibiotics, oral antibiotics, dapsone, retinoids, ciclosporin, and anti-androgens. The modelled proportions of each component are presented in further detail in Section 4.2.8.1. The company argue that despite the present decision problem definitionally excluding adalimumab as a comparator (i.e. following failure or contraindication to adalimumab), 20.8% of patients on BSC would in fact continue to receive adalimumab despite lack of efficacy. This figure was based on an international survey of HS patients between October 2017 and July 2017.[22] The

company also state that a consultant dermatologist practicing in England confirmed that 'in the absence of alternative options, patients would continue with biologic treatment if they had a minimal level of response'. A proportion of patients on BSC are therefore modelled include costs and HRQoL benefits associated with adalimumab.

Notably, the company's model does not distinguish between BSC as a comparator and BSC as a subsequent therapy with regards to the inclusion of adalimumab. That is, it is assumed that following the discontinuation of bimekizumab or secukinumab, 20.8% of patients will re-initiate treatment with adalimumab.

Points for critique

The EAG does not consider it appropriate to include adalimumab as a component in BSC following discontinuation of bimekizumab or secukinumab. In response to Clarification Question B8, the company stated that "…patients who lose response when no more effective treatments are available could remain on current therapy with declining response, undertake re-treatment of a previously effective drug or receive BSC only." The EAG considers it plausible that a proportion of patients may *continue* to receive a biological therapy following loss of response, the re-initiation of a non-indicated treatment appears unlikely in comparison. It is the EAG's understanding that the re-initiation of adalimumab following loss of response to secukinumab is unlikely to be reimbursed on the NHS, and thus the EAG considers this usage highly unlikely. The EAG therefore considers the inclusion of adalimumab in BSC when used subsequent to bimekizumab or secukinumab inappropriate. The EAG also notes clinical advice to the company and EAG which indicates that patients would continue to receive a biologic following partial loss of response in the absence of further active treatment options. The company state that 'assuming that a proportion of patients would receive secukinumab or bimekizumab would bias the economic model', but no justification was provided for this argument. The EAG therefore presents a scenario in Section 6.2 in which BSC following loss of response to bimekizumab and secukinumab is continued in 20.8% of patients.

The EAG note that there appears to be a weaker treatment effect on the bimekizumab Q4W dosing regimen in those with prior biologic experience, however, the sample size for this population is small. As this is the dosing and population most relevant to NHS practice and thus the decision problem, this represents an area of uncertainty. This issue is discussed further in Sections 2.3 and 4.2.6.

The company model assumed a constant dose (Q4W) for secukinumab, despite the marketing authorisation allowing for a titrated (Q2W) dose following a lack of response. If this approach to treatment leads to improved outcomes, the model may underestimate the efficacy of secukinumab. However, the effect of up-titration is uncertain, as dose-response relationships were unclear for secukinumab. In their clarification response, the company present the results of a scenario which

implements an approximation of this approach based on an extension of Q2W treatment to Week 48 and the relaxation of the stopping rule for non-response. The company in TA935 allowed up-titration only to Week 28, following 12 weeks of Q2W treatment. This scenario functionality was not built into the model accompanying the clarification response and was not provided in time to be validated or integrated into the EAG Report.

As discussed in Sections 4.2.2, 4.2.6 and 4.2.8.1, the EAG note that stopping rules for secondary non-responders have been established in TA392 and TA935 and agreed upon by the committee. Bimekizumab and secukinumab should only be discontinued when a patient stops responding during the maintenance phase and does not re-establish a response for 12 weeks. In the TA935 final draft guidance (FDG), the committee describe clinical expert opinion stating that if a patient stops responding to treatment, they would add in additional treatments such as antibiotics or surgery, and only stop treatment if the patient continued to not respond. If a patient regains response within this period, they should continue to receive their current active treatment. This was the accepted method of implementation of the stopping rule for secondary non-responders in TA935. In assuming that patients discontinue treatment with bimekizumab and secukinumab immediately upon losing response, the company's base-case analysis may significantly underestimate total treatment costs and underestimate the proportion of patients benefiting from treatment over time.

4.2.5 Perspective, time horizon and discounting

The model adopted a lifetime (60-year) time horizon, at which point 1.37% of patients in the bimekizumab arm remained alive, with a population age of 96.65 at the end of the modelled period. In scenarios which relax assumptions around disease-related mortality rates, up to ~4% of patients remain alive at the end of the time horizon. Whilst unlikely to make a significant difference to model results, a 'lifetime' time horizon should encompass the full lifespan of the patient population. The EAG examines the impact of a 70-year time horizon in Section 6.2.

The model applied a discount rate of 3.5% per annum for costs and benefits and adopted an NHS and Personal Social Services perspective. The model had a cycle length of four weeks and applied a half-cycle correction.

4.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness is represented in the model through transition probabilities which govern the movement of the bimekizumab, secukinumab, and BSC cohorts through the model health states described in Section 4.2.2. Transition probabilities were derived primarily from the BE HEARD I and II trials for the bimekizumab treatment arm. In the company's base-case analysis, effectiveness was based on data from biologic-experienced and biologic-naïve according to the distribution observed in

the trial. For the comparators, the general approach taken by the company (discussed in detail below) was to apply risk ratios (RRs) obtained from the NMA described in Section 3.9 for each HiSCR level (informing the relative efficacy of comparators) to the bimekizumab transition probabilities. The RRs used to calculate the transition probabilities for BSC during the initial treatment phase were based on the placebo arm of BE HEARD.

In the company's clarification response, transition probabilities for the biologic-experienced and biologic-naïve subgroups were also presented. As these values are not applied in the company's base-case analysis, they are not reproduced in the following section, but can be found in the company's response to CQ B16. Scenario analyses exploring the impact of using effectiveness data based on biologic experienced patients could not be presented in Section 6, as this model functionality or appropriate model inputs to perform subgroup analysis was not provided by the company upon request.

4.2.6.1 Derivation of transition probabilities

Bimekizumab

In response to CQ B14, the company provided details of the methods used to estimate bimekizumab transition probabilities from BE HEARD trial data. The company's approach to estimating transition probability matrices from trial data for bimekizumab was as follows. Each patient was assumed to start in the non-response state (HiSCR<25) at week zero. For each subsequent visit, each patient was assigned a HiSCR state (thus 4-weekly transitions exist for each patient). A generalised logit model (GLM) was employed where the response variable was the "to" state and the explanatory variable the "from" state. The probabilities estimated by the GLM model for each imputation were averaged to obtain final estimates used in the transition probability matrices.

Secukinumab and BSC

To derive the transition probabilities for secukinumab and BSC, the company used the respective RRs versus bimekizumab for the HiSCR50, HiSCR75, and HiSCR90 outcomes, as estimated in the NMA to adjust the corresponding bimekizumab probability (see Section 3.9). The company assumed that probabilities would be exclusive and exhaustive as well as applying additional constraints (detailed in CS Table 57). Placebo outcomes were used to represent BSC. A full description of the company's methods is in provided in B.3.3.2 of the CS.

The company's method for deriving transition probabilities varied according to treatment phase and so the derivation of probabilities for each phase are discussed in the following sections.

Initial treatment phase (first 16 weeks)

The company used bimekizumab Q2W outcomes from BE HEARD I and II (both the Q2W/Q2W and

Q2W/Q4W arms) to calculate (4-week) transition probabilities for the treatment phase using the GLM method described above. The estimated transition probabilities are reproduced in Table 22 below.

Table 22 Initial phase transition probabilities - bimekizumab (<Week 16) (CS Table 56, Page 134)

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

To derive the secukinumab transition matrix, the company used the corresponding RRs versus bimekizumab as estimated in the NMA (see Section 3.9) for HiSCR50, HiSCR75, and HiSCR90 (procedure described above). The company described how in the absence of RRs for HiSCR25 for secukinumab, it was assumed that the ratio of probabilities for non-response versus HiSCR25 for bimekizumab were the same for secukinumab. The corresponding values are reproduced in Table 23.

Table 23 Initial phase transition probabilities - secukinumab (<Week 16) (extracted from company's executable model)

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The same approach was adopted to derive a transition matrix for the BSC arm by using the RRs of placebo versus bimekizumab from BE HEARD I and II with corresponding transition probabilities shown in Table 24.

Table 24 Initial phase transition probabilities for BSC (<Week 16) (extracted from company's executable model)

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Maintenance phase (Weeks 16 - 48)

The same procedure as described above was repeated to derive bimekizumab transition probabilities for the maintenance phase. The analysis only included data from patients with at least a partial response (HiSCR25) at Week 16 using data from patients randomised to Q2W/Q4W from BE HEARD. Using the same procedure as above, RR values based on the initial phase of the NMA were applied to the bimekizumab probabilities to derive the transition matrix for secukinumab, in the absence of a common comparator for the maintenance phase of the respective trials. This assumes the same relationship exists between initial response on bimekizumab and secukinumab, and the long-term maintenance of response.

The corresponding probabilities for bimekizumab and secukinumab are shown in Table 25 and Table 26, respectively.

Table 25 Maintenance phase transition probabilities - bimekizumab (Weeks 16-48) (CS Table 58, Page 135)

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 26 Maintenance phase transition probabilities - secukinumab (Weeks 16-48) (extracted from company's executable model)

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For the BSC model arm, the company assumed that patients invariably experience gradual loss of any response they have achieved by Week 16. That is, at each cycle during the maintenance treatment period, patients on BSC could only remain in their current health state, or experience deterioration in their level of response. The company justified this assumption with reference to clinical advice, which suggested it was unlikely to expect improvements in a patient's condition on BSC. Transition probabilities for improvement or maintenance of response level were informed by the BSC transition matrix derived from the placebo arm of BE HEARD I and II for the initial treatment phase. Transitions to a higher level of response were simply set to zero (see Table 27), and the remaining probabilities were renormalised. These transitions also apply to patients who discontinue bimekizumab and secukinumab between Weeks 16 and 48.

Table 27 Four-week transition probabilities for BSC (weeks 16-48) (CS Table 59, Page 135)

	Transitions To				
Transitions From	HiSCR<25	HiSCR 25-<50	HiSCR 50-<75	HiSCR 75-<90	HiSCR 90+
HiSCR<25	[redacted]	0	0	0	0
HiSCR 25-<50	[redacted]	[redacted]	0	0	0
HiSCR 50-<75	[redacted]	[redacted]	[redacted]	0	0
HiSCR 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	0
HiSCR 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Clinical advice provided to the EAG described HS as a condition characterised by periods of transient exacerbation and improvement. The EAG were concerned that the company's application of assumption of gradual deterioration does not appropriately capture the natural history of HS and will rapidly overestimate the proportion of non-responders on BSC. In response to CQ B17 which outlined these concerns, the company argued that this approach was consistent with the opinion of the clinical

advisors in attendance at the TA935 committee meetings, based on the concept that BSC patients cannot maintain long-term response in the way that BSC was modelled in TA392 and in EAG scenarios conducted in TA935. They also argue that this approach was consistent with the advice received by the company from two UK advisory boards.

In the CS and in response to CQ B17 the company provided a number of alternative scenarios for the 16–48-week BSC transition probabilities based on the following assumptions and data sources:

- Gradual deterioration (base-case): based on the placebo arm from the BE HEARD studies, adjusted so patients cannot improve their response;
- PIONEER II 36-week placebo data;
- Week-16 NMA against placebo to estimate BSC efficacy;
- Long-term loss of response based on linear fit to PIONEER II.

Long-term effectiveness (post-Week 48)

The long-term (post-Week 48) transition probabilities applied in the model for the active treatment arms (bimekizumab and secukinumab) were assumed to be the same as for the maintenance phase. These transition probabilities were applied for the remainder of the modelled time horizon.

To represent the progression of patients between states in the BSC arm after Week 48, the company assumed that patients would experience a 'durable response', that is, they would maintain their 48-week response level indefinitely and only leave their health state due to all-cause discontinuation or death. This approach was adopted in TA392 in the absence of alternative data sources for BSC. However, the TA392 model directly applied observed effectiveness data from PIONEER II for placebo during Weeks 16-48, meaning a much larger proportion of patients were in response health states by (and thus beyond) Week 48.

Summary

A summary of data sources and assumptions used to inform transition probabilities in each model phase is presented in Table 28 below.

Table 28 Summary of company base-case efficacy assumptions by model phase

Model phase	Model cohort		
	Bimekizumab	**Secukinumab**	**Best supportive care**
Treatment phase (first 16 weeks)	Transition probabilities derived based on Q2W data from intervention arm of BE HEARD (Q2W/Q2W, Q2W/Q4W)	RRs from NMA used to adjust bimekizumab transition probabilities	RRs from NMA (placebo arm of BE HEARD) used to adjust bimekizumab transition probabilities

Maintenance phase (weeks 16-48)	Transition probabilities derived based on Q4W data from intervention arm of BE HEARD (Q2W/Q4W)	RRs from NMA used to adjust bimekizumab transition probabilities	Probabilities from treatment phase adjusted to incorporate gradual deterioration assumption
Post 48-weeks	Same as for maintenance phase	Same as for maintenance phase	Assumption that patients maintain their response level attained at week 48 indefinitely

A comparison of health state residence over time across each treatment arm in the model is depicted in Figure 9. The first set of graphs illustrates the long-term impact of the 'durable response' assumption on the proportion of responders on each treatment. The vast majority of QALY gain attributed to active treatment arises from the assumption that once on BSC, patients remain in their current health state indefinitely. The second set of plots illustrates the effect of the 'gradual decline' assumption without also assuming that outcomes are maintained indefinitely from Week 48.

Figure 9 Comparison of health state residence over time in company's executable model (A) 'durable response' (company base-case) (B) 'gradual decline' from Week 48

A

B

Points for critique

Choice of transition probability data sources

As discussed in Section 4.2.3, the company's base-case pooled efficacy data from patients both with and without previous biologic exposure. The BE HEARD studies included only 191 (18.8%) biologic-experienced patients, whose outcomes, as discussed in Section 3.4, were consistently (but not significantly) poorer than biologic-naïve patients. There appeared to be a larger negative effect of prior biologic exposure in the maintenance treatment phase outcomes than those in the initial phase. Given the positioning of bimekizumab in this appraisal, the NHS population is likely to comprise almost exclusively patients with previous exposure to adalimumab. The EAG therefore requested a

model scenario (CQ B16) whereby transition probabilities were based on the relative effectiveness of treatment given the proportions of biologic-naïve/experienced patients in the NHS population. In their response, the company stated that they did not identify any evidence on the distribution of biologic-naïve/experienced patients in the NHS population. Instead, the company provided subgroup analyses based on previous biologic exposure, indicating a small increase in the ICERs for the biologic-exposed subgroup, albeit subject to significant uncertainty. The EAG consider it appropriate to align the source of efficacy data to the population described in the decision problem, and consider subgroup results specific to the biologic experienced population relevant for decision making. The EAG also considers the distribution of the NHS HS population according to prior biologic exposure to be a source of uncertainty.

Source of data for BSC transition probabilities

The EAG have concerns with the company's imposition of constraints on the progression of BSC patients in both the maintenance phase, where patients can only maintain or lose their current level of response, and in the post 48-week phase where patients are assumed to maintain their attained response level indefinitely ('durable response' assumption).

It is the EAG's understanding that the course of HS is characterised by periods of improvement and exacerbation. In practice, exacerbations may be managed with antibiotics or surgery, whether a patient is on active treatment or BSC. The model accounts for the costs of multiple surgeries and procedures over a patient's lifetime, and it seems implausible that these procedures would offer no benefit in terms of improving a patient's symptom burden. The continued use of biologics in the mix of BSC treatments, argued by the company to occur in practice due to their clinical utility, also runs contrary to the idea that it is impossible to establish or re-establish response beyond 16 weeks of initiating treatment.

The 'gradual decline' approach also has the effect of increasingly underestimating the observed outcomes of patients on the BSC arm over time, thus overestimating the relative benefits of active treatment. This means that while sustained and significant improvements may not be realistic on BSC for an individual patient, the fluctuating natural history of HS means that a relatively stable percentage of patients may be responding at any given time. This is evident in comparisons of BSC health state residence predicted by the model under alternative assumptions around the effect of BSC. Table 29 compares the proportion of patients on BSC with a HiSCR50 response between Week 20 and Week 36 under the company's 'gradual deterioration' base-case assumption, observed placebo data in PIONEER II, a 'loss of response only' scenario which applies a linear model to PIONEER II placebo loss of response data, and a scenario in which initial period RRs from the NMA for placebo vs bimekizumab are applied to bimekizumab maintenance transition probabilities.

Table 29 Comparison of >HiSCR50 response on BSC over time under alternative assumptions (Clarification Response Table 57 and executable model)

Time (weeks)	PIONEER II	Gradual deterioration (base case)	Loss of response only	NMA
20	23.2%	[redacted]	[redacted]	[redacted]
24	25.2%	[redacted]	[redacted]	[redacted]
28	15.2%	[redacted]	[redacted]	[redacted]
32	18.5%	[redacted]	[redacted]	[redacted]
36	15.9%	[redacted]	[redacted]	[redacted]
40	NR	[redacted]	[redacted]	[redacted]
44	NR	[redacted]	[redacted]	[redacted]
48	NR	[redacted]	[redacted]	[redacted]

These data show that the company's base-case assumption results in a substantial underestimate of the proportion of responders on BSC when compared with observed placebo data from PIONEER II ([redacted] vs 15.9%). However, the EAG considers the most appropriate sources of maintenance phase transition probabilities for BSC to be those generated using the NMA, with observed values in PIONEER II representing the lower bound of plausible response to BSC. Whilst the proportion of responders at Week 36 using the NMA is somewhat higher than observed in PIONEER II using this method, it is not unreasonable to assume that a larger placebo effect in the BE HEARD studies may have been observed relative to that in PIONEER II. The latter study was undertaken before there were any active treatment options for HS, and it is an often-observed phenomenon that placebo response rates improve over time as care and expectations of care improve. Indeed, the bimekizumab treatment response rates will also comprise an element of placebo effect which is specific to the setting of the trial, and so should be accounted for in estimates of the relative treatment effect. Furthermore, the committee in TA935 considered response to placebo in PIONEER II to underestimate placebo response in an NHS setting, as there is a much wider range of treatments offered as part of BSC in NHS practice than were available to patients in PIONEER II. Furthermore, as the company assume that BSC comprises active treatment for 20.8% of patients, it is not overly conservative to apply a higher estimate of response on placebo. The EAG therefore favours the use of the NMA to adjust bimekizumab maintenance phase transition probabilities to derive those for BSC. Scenario analyses exploring the effect of alternative assumptions regarding BSC efficacy are presented in Section 6.

Whilst the company stated that the assumption of a 'durable response' to BSC was modelled in TA392, the EAG note that the committee considered the alternative plateaus in response rates for the BSC arm presented by the EAG and company to lack face validity in TA935. The EAG does not object in principle to the application of a plateau to response rates on BSC, however, the method by

which the company have applied this assumption in the model introduces very substantial bias in favour of bimekizumab. As discussed in Section 4.2.2, as BSC transitions are fixed beyond Week 48 of the model time horizon, patients who discontinue bimekizumab and secukinumab for 'other reasons' will maintain their response level at Week 48 (or at the point of discontinuation if this occurs beyond Week 48) for the remainder of the time horizon. Non-responders who switch to BSC are subject to initial treatment period transition probabilities, and if they go on to achieve a response, this may also be maintained indefinitely. This assumption results in response rates of around [redacted] in the bimekizumab arm in perpetuity, despite >99% of patients having discontinued active treatment. It may be inappropriate to apply initial response rates to placebo to patients discontinuing active treatment, which imply a significant boost to response rates. A large component of the placebo response in a trial setting is a patient's belief that they are receiving a new effective therapy. For patients in an NHS setting who are unblinded to the fact they are no longer receiving an active treatment, it may be inappropriate to apply transition probabilities representative response to placebo. Instead, it may be more appropriate to apply transition probabilities representing the long-term natural history of the condition to patients who may The EAG explores a scenario in which maintenance phase response rates are instead applied to patients who discontinue treatment.

When BSC maintenance phase transition probabilities are applied beyond Week 48, bimekizumab incremental QALYs versus secukinumab and BSC are reduced by ~75%. As previously described in Section 4.2.2, the 'durable response' assumption on BSC should only be applied using appropriately implemented tunnel states to ensure the effect of treatment does not persist in patients who discontinue active treatment. The EAG considers scenarios in which the maintenance phase transition probabilities for BSC are applied beyond Week 48 to provide an informative assessment of the relative effectiveness of each treatment option.

4.2.6.2 Treatment discontinuation

There are three sources of discontinuation represented in the model for bimekizumab and secukinumab: 1) primary non-response (discontinuation due to non-response at 16 weeks); 2) secondary non-response (discontinuation due to non-response post 16-weeks), and discontinuation for any other reason such as adverse events. The consequences of discontinuation are that patients immediately switch to BSC costs, utilities, and transition probabilities. Each of these is discussed in turn below.

Treatment discontinuation in the company's base-case analysis is depicted in Figure 10 alongside response rates, illustrating the assumption that a much larger proportion of patients treated with active therapies at this treatment line will receive permanent benefits relative to BSC, well beyond the point of discontinuation.

Figure 10 Comparison of discontinuation with ongoing treatment response in company base case

Discontinuation due to non-response (primary and secondary)

The company allowed patients to discontinue from active treatments (bimekizumab and secukinumab) as a result of non-response. This included patients who had no response at 16-weeks (primary non-response) and those who experience loss of response (i.e., by transitioning into the non-response state) at any point after the Week 16 assessment. Primary and secondary non-responders were treated in the same way in the model, where discontinuing patients are subject to BSC costs and outcomes from the next model cycle onwards.

The CS describes a stopping rule for patients on secukinumab where treatment is only ultimately withdrawn for non-responders when a patient has remained in the non-response health state for 12 consecutive weeks. This is the EAG's understanding of the committee's preference for modelling secondary non-response in TA935 and aligns with clinical advice received by the EAG. However, this understanding did not appear to be implemented in the executable model accompanying the submission. In response to CQ B2, the company stated that the description of a tunnel state for secondary non-response included in the submission was in error, and that discontinuation was modelled as intended. Furthermore, the company stated that their understanding of the stopping rules implemented in TA935 were that they applied only during up-titration as part of the secukinumab licence. As a result, they included a scenario in which the stopping rule for patients who do not achieve a response (or lose response to) secukinumab is relaxed so only a proportion of patients experiencing non-response discontinue.

Discontinuation for any other reason

As described above, the company allowed for discontinuation for reasons other than those explicitly represented in the stopping rule described above. The risk was applied to all patients regardless of their current response category. In the original executable model, the company applied a per cycle 'all cause' discontinuation rate of [redacted] per four-week cycle, which was based on the total number of patients who discontinued treatment between Weeks 16 and 48 in the BE HEARD study. In CQ B3, the EAG suggested this could result in double counting of discontinuation, as this figure was likely to include those who discontinued due to loss of response. In the updated company base case submitted

with their clarification response, the company apply a per-cycle probability of discontinuation for other reasons of [redacted], based only on the number of patients who discontinued treatment in BE HEARD due to an adverse event. The company noted that this value was similar to the 0.47% applied in Corbett *et al*. 2016,[23] the source of the company's long-term (>48 week) discontinuation probability.

Points for critique

The EAG consider primary non-response to have been modelled appropriately, and in alignment with the committee's preferences in previous appraisals.

However, the company's approach to modelling patients who discontinue active treatment due to secondary non-response is an incomplete representation of accepted stopping rules, and the way in which these treatments are used in clinical practice. As described above, the company modelled patients to discontinue active treatment and receive BSC costs and outcomes immediately upon loss of response. Section 3.11 of the TA935 FDG very describes the stopping rule accepted by the committee for secondary non-response to secukinumab as follows:

"*Secukinumab is stopped in people whose HS stops responding to secukinumab in the maintenance phase and non-response is maintained for 12 weeks (this was applied in the model using tunnel states to track when people entered the no-response health state)"*

This was explicitly *not* referring to up-titration as stated by the company in their clarification response. As has been discussed previously, clinical advice to the committee and the EAG describes that patients are likely to be evaluated over a period of at least 12-weeks before active treatment is stopped. During this period, clinicians will attempt to re-establish a response through the use of additional treatments and surgical interventions. Through failing to implement this stopping rule, the company's base-case analysis will (potentially significantly) underestimate treatment costs and the proportion of patients who regain and retain a response to bimekizumab and secukinumab.

The EAG considers the omission of the opportunity for patients to regain response rather than immediately discontinuing to substantially overestimate the rate of discontinuation on active therapy. As is discussed elsewhere, HS is characterised by periods of exacerbation and remission, established through a range of pharmaceutical and surgical management strategies. This applies equally during treatment with an active therapy and is reflected in the transition probabilities generated using the BE HEARD study data. In any given cycle during the maintenance treatment period and beyond, a non-responder on bimekizumab should have a probability of around [redacted] of regaining at least a partial response on the basis of the BE HEARD transition probabilities. In assuming these patients discontinue treatment immediately, the model predicts that around [redacted]% of patients entering the

maintenance phase with at least a partial response will have discontinued at Week 48, compared to only [redacted] over the equivalent period in the BE HEARD studies. This means a substantial component of the treatment effect, i.e. the ability to regain and maintain a response, is omitted from the model. This introduces very substantial uncertainty into the results and means total and relative QALY gain on each treatment option cannot be ascertained in the current model structure. The EAG considers this a key uncertainty.

Using the transition probability representing a patient remaining in non-response over three cycles, around [redacted] would remain in the non-response state on bimekizumab, and [redacted] on secukinumab. If we assume that this is broadly representative the proportion of patients in the non-response state who would discontinue treatment in a given 12-week period, this produces a per cycle probability of [redacted] of discontinuation in the non-response health state on bimekizumab, and [redacted] on secukinumab. In Section 6.2, the EAG explores a scenario in which discontinuation probabilities for those in the non-response health state are changed from 100% per the company base case to 20%. The use of the values derived from the transition probabilities may be unfair to bimekizumab, as this scenario cannot ensure those who do not maintain non-response do indeed regain response. This emphasises the need to implement this stopping rule in full.

The EAG considers the per cycle probability of discontinuation for 'other reasons' applied in the updated company base-case analysis to be appropriate. As previously discussed in Section 4.2.2, the EAG had concerns regarding the treatment of patients who discontinue for 'other reasons', as this appeared to apply a permanent treatment effect for many patients (as can be seen in Figure 10 above). It is clearly inappropriate for such a large proportion of patients to experience a permanent treatment effect beyond the point of discontinuation. It was unclear from the company's description of the model, and the executable model itself, whether patients were subject to BSC outcomes for 48 weeks following discontinuation. Scenarios exploring alternative assumptions regarding the treatment of patients who discontinue for other reasons are presented in Section 6.

4.2.6.3 Mortality

Mortality is modelled through the application of general population mortality rates to patients occupying all response health states (obtained from Office for National Statistics life tables). Additionally, a standardised mortality ratio (SMR) representing excess mortality associated with uncontrolled HS is applied to the non-response (i.e. HiSCR<25) health state. This contrasts with the approaches adopted in TA392 and TA935, in which general population mortality rates were applied to all patients regardless of response level.

The crude SMR applied to represent disease-related mortality (1.86) was obtained from an epidemiological study of patients with HS in Korea,[24] and was based on a subset of these patients who

had previously undergone surgical procedures, capturing 90-day acute surgical mortality. This study also reported an adjusted SMR (1.48) which accounted for current smoking status, drinking status, body mass index, Charlson comorbidity index, and the presence of psychiatric diseases at the index date. The EAG requested that the company justify the use of the crude HR over this adjusted value (CQ B4.c), but no response was provided.

In CQ B4, the EAG also questioned the company's assumption that only patients in the non-response state experience disease-related mortality. It is the EAG's understanding that mortality in this population is driven by longstanding comorbidities linked to obesity, diabetes, and heart disease. Patients may therefore not immediately relieved of this additional mortality risk following treatment response. In response to CQ B4, the company stated that they have not identified any evidence on the distribution of mortality risk by HiSCR level. They also stated that their assumption is that severity of HS is a causal factor in comorbidities that contribute to increased mortality. Hence, individuals with worse response levels to treatment would be expected to face higher mortality risk, while patients with better response levels would face a lower mortality risk. The company stated that they consider the current base-case may underestimate the mortality risk for those with the most severe disease.

Points for critique

The EAG had concerns about the company's application of mortality in the model. Clinical advice provided to the EAG suggested that a response to treatment did not mean a patient was immediately no longer subject to excess mortality related to HS and the typically long-standing combination of co-morbidities, and indeed patients treated with adalimumab still continue to suffer with co-morbidities. The company's assumption that excess mortality is only experienced by patients while in the *non-response* state (thus assuming only non-responders experience disease-related mortality) may therefore lack clinical plausibility. The model allows for frequent movement between the response (and non-response) health states meaning that a patient who is an initial non-responder but who then experiences a response (at any HiSCR level), would see their mortality risk return to that of the general population despite their comorbid conditions.

The EAG understands that the mortality risk attributable to particular co-morbidities, in particular the psychological aspects of living with HS, may be reduced or eliminated following adequate treatment response. However, the mortality risk associated with other co-morbidities, such as cardiac issues, diabetes, and stroke is likely to apply for extended periods. It is also unclear whether a response at the lowest response level (HiSCR25) would have the same beneficial impact on mortality as a response at HiSCR90. Given these uncertainties, the EAG explore a number of scenarios in Section 6.2, namely; 1) general population mortality for all patients; 2) the adjusted SMR of 1.48 from Lee *et al*. used for all patients. The impact of response to biologics upon mortality risk remains a key area of uncertainty.

Evidence on the relationship between duration of response and reduction in the burden of co-morbidities in HS may inform a more sophisticated implementation of mortality in the model.

4.2.6.4 Adverse events

The company's base-case analysis did not explicitly consider the cost or HRQoL implications of adverse events. The company argued that the AE profile of bimekizumab was sufficiently similar to that of secukinumab to exclude the independent consideration of AEs, and that AEs had not been considered in the TA935 company model.

Points for critique

The EAG notes that the cost and utility consequences of adverse events were included in the preferred set of assumptions on the EAG model in TA935, however, the committee did not express a position on this issue in the FDG. The EAG consider it likely that the differential utility and resource implications on secukinumab and bimekizumab will be small. For further discussion of this issue, see Section 4.2.8.3.

4.2.7 Health related quality of life

The BE HEARD I and II studies collected EQ-5D-3L data directly from patients throughout the trial period. Repeated measure analysis of covariance (ANCOVA) models were fitted to the trial data to derive utility estimates by HiSCR response state, treatment arm, and treatment period (initial vs maintenance).

This approach generated separate utility sets for biologic treatment (bimekizumab, secukinumab, and adalimumab) and BSC. The company argued that in TA935, it was accepted that trial data demonstrated a statistically significant HRQoL benefit on secukinumab relative to placebo within most HiSCR categories. Model coefficients are reproduced in Table 30 below. In this analysis, a significant treatment effect upon EQ-5D was only observed in the non-response and high response categories. The company considered this sufficiently supportive of an assumption of treatment-specific utility sets in the model.

Table 30 EQ-5D-3L ANCOVA model coefficients (CS Table 62, Page 140)

Covariate	Fixed Effect	Estimate	SE	p-value
	Intercept	[redacted]	[redacted]	[redacted]
Baseline EQ-5D Utility	Baseline EQ-5D Utility	[redacted]	[redacted]	[redacted]
Age	Age	[redacted]	[redacted]	[redacted]
Sex (Reference Category: Male)	Female	[redacted]	[redacted]	[redacted]
Response State (Reference Category: Non-Response)	Partial Response	[redacted]	[redacted]	[redacted]
	Response	[redacted]	[redacted]	[redacted]
	High Response	[redacted]	[redacted]	[redacted]
	Very High Response	[redacted]	[redacted]	[redacted]
Interaction Between Treatment and Response State BKZ Total (Reference Arm: Placebo)	Non-Response	[redacted]	[redacted]	[redacted]
	Partial Response	[redacted]	[redacted]	[redacted]
	Response	[redacted]	[redacted]	[redacted]
	High Response	[redacted]	[redacted]	[redacted]
	Very High Response	[redacted]	[redacted]	[redacted]

Additionally, the company favoured further splitting utilities by treatment period, observing small (but consistent) numerical improvements in observed utilities in the maintenance treatment period compared to the initial period. The EAG requested evidence specifically in support of the statistical significance of this difference across treatment phase (CQ B5), but no response was provided by the company. The health state utilities applied in the company's base-case analysis are presented in Table 31.

Table 31 Health state utilities in company base-case analysis (CS Table 60, Page 138, and executable model)

Response health state	Biologics mean utility (SE)	Best supportive care mean utility (SE)
Initial treatment period		
Non-response (HiSCR<25)	[redacted]	[redacted]
Partial response (HiSCR25)	[redacted]	[redacted]
Response (HiSCR50)	[redacted]	[redacted]
High response (HiSCR75)	[redacted]	[redacted]
Very high response (HiSCR90)	[redacted]	[redacted]
Maintenance treatment period		
Non-response (HiSCR<25)	[redacted]	[redacted]
Partial response (HiSCR25)	[redacted]	[redacted]
Response (HiSCR50)	[redacted]	[redacted]
High response (HiSCR75)	[redacted]	[redacted]
Very high response (HiSCR90)	[redacted]	[redacted]

The base case applied different utilities for the initial and maintenance treatment periods, which the company argued represented the idea that HRQoL improves over time whilst patients remain on treatment. Utilities for secukinumab were assumed to be the same as those for bimekizumab. BSC utilities during the initial treatment period were based on the placebo arm of the BE HEARD I and II studies. The maintenance period BSC utilities were weighted based on the proportion of patients assumed to be treated with adalimumab, i.e. the bimekizumab maintenance utility was applied to 20.8% of patients, with the BSC induction utility applied to 79.2% of patients. Utilities were adjusted over time using the general population value set reported by Hernández Alava *et al*.[25] to reflect the impact of aging on HRQoL.

Points for critique

The EAG made several requests for further information and reanalysis of EQ-5D-3L data from the BE HEARD studies. These requests primarily related to producing an alternative to the treatment arm- and treatment phase-specific utility sets in the company's base-case analysis.

Whilst the EAG acknowledges the clinical rationale for treatment specific utilities, i.e. that active treatments may offer superior symptom control beyond that which can be captured by the HiSCR outcome, this was not consistently borne out statistically in the trial data for bimekizumab. Utility benefits over placebo for patients on bimekizumab were only significant in the non-response and high response health states in the company's ANCOVA model. This results in a utility benefit of [redacted] for non-responders on bimekizumab compared to BSC. As can be seen in Table 31, the application of treatment-specific utilities results in patients with a high response to BSC having a similar utility to non-responders on bimekizumab. However, there were only a small number of observations for high response to BSC available upon which to base utility values. The EAG requested data on the number of patients contributing data to each health state utility, but the company provided only the number of observations [redacted], which include repeat measurements, for the high response category, and [redacted] observations for the response (HiSCR50) category. These utilities may therefore be driven by the individual HRQoL of a very small numbers of patients, resulting in logically inconsistent values (i.e. a high response utility [redacted] lower than that of the partial response [redacted] and response [redacted] categories). The EAG consider a scenario in which utilities based on level of response alone may be plausible, applying only the treatment-specific (i.e. statistically significant) utility for non-responders, recognising that biologic-treated patients may receive some benefit short of a HiSCR25 response. This scenario is presented in Section 6.2.

Whilst utilities recorded during the maintenance treatment phase were consistently higher by response state than those recorded during the initial phase, there was no evidence that these differences achieved statistical significance. The EAG therefore considers the use of pooled utilities per TA935,

regardless of treatment phase, a plausible alternative approach. This scenario is presented in Section 6.2.

The company's base-case analysis did not weight BSC initial period utilities for the inclusion of adalimumab. This appears to be inconsistent with the argument that patients treated with biologics will have improved HRQoL. The EAG presents a scenario in Section 6.2 in which BSC utilities are weighted for adalimumab use during the initial treatment phase.

4.2.8 Resources and costs

The CS provided a description of resource use and costs applied in the model. This included drug acquisition and administration costs and costs associated with management of the condition.

The company undertook a literature review to identify relevant cost and resource use data for moderate-to-severe HS, identifying two studies which provided evidence from the UK. The company stated that as the response states applied in these studies did not align with the mutually exclusive health states considered in their cost-utility analysis, they concluded that TA392 and TA935 were the most appropriate sources of cost and resource use data.

Points for critique

The EAG is satisfied that the previous appraisals represent the most appropriate published source of resource use information.

4.2.8.1 Drug acquisition and administration costs

Dosing schedules and modelled costs for bimekizumab and secukinumab are summarised in Table 32

Modelled dosage	**Number of doses per cycle**		
	First cycle (initial)	**Cycle 2, 3, 4 (initial)**	**Maintenance cycles**
Bimekizumab: 320 mg Q2W for 16 weeks followed by maintenance therapy 320 mg Q4W.	2	2	1
Secukinumab: 300 mg at Weeks 0, 1, 2, 3, and 4, followed by Q4W	5	0.9199*	0.9199*
Acquisition costs			
Bimekizumab 320 mg Q2W/Q4W	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg Q4W	£6,093.90	£1,121.18	£1,121.18
Administration costs			
Bimekizumab 320 mg Q2W/Q4W	1 hour nurse visit (£47.39)	The model assumed patients self-administer subsequent injections.	
Secukinumab 300 mg Q4W/Q2W			

*This was corrected to 1 dose per cycle in the EAG-corrected company base case

, dose and frequency were based on the respective EMA summary of product characteristics (SmPC) for each drug. All treatment arms also included a range of concomitant medications, whose use relates to symptom management, which is presented separately in Table 33.

Each dose of bimekizumab comprises two 160 mg prefilled syringes. Bimekizumab is currently available to the NHS with a confidential patient access scheme (PAS) discount. Acquisition costs presented in and elsewhere in this report are inclusive of this commercial arrangement. The modelled dose for bimekizumab is 320 mg Q2W during the 16-week initial treatment period, followed by maintenance treatment comprising 320 mg Q4W.

Secukinumab can be administered as either a 300 mg/2 ml pre-filled injection pen, or as two 150 mg/1 ml pens. The list price of secukinumab is £1,218.78 per dose in either case. The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3, and 4, followed by maintenance dosing Q4W. The company interpreted this as 'monthly' dosing in the model, meaning maintenance secukinumab was administered 0.9199 times per cycle. Secukinumab is available to the NHS with a PAS discount which is commercial in confidence. Pricing and results considering all available commercial arrangements are presented in a confidential appendix to this report.

The only cost associated with treatment administration for bimekizumab and secukinumab is a one-hour visit from a Band 6 nurse to train patients to self-administer the subcutaneous injections. The make-up and costs of concomitant medications (i.e. best supportive care) are discussed separately below.

Table 32 Modelled drug dosing and acquisition costs per cycle (adapted from CS Table 64, Page 85)

Modelled dosage	Number of doses per cycle		
	First cycle (initial)	Cycle 2, 3, 4 (initial)	Maintenance cycles
Bimekizumab: 320 mg Q2W for 16 weeks followed by maintenance therapy 320 mg Q4W.	2	2	1
Secukinumab: 300 mg at Weeks 0, 1, 2, 3, and 4, followed by Q4W	5	0.9199*	0.9199*
Acquisition costs			
Bimekizumab 320 mg Q2W/Q4W	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg Q4W	£6,093.90	£1,121.18	£1,121.18
Administration costs			
Bimekizumab 320 mg Q2W/Q4W	1 hour nurse visit (£47.39)	The model assumed patients self-administer subsequent injections.	
Secukinumab 300 mg Q4W/Q2W			

*This was corrected to 1 dose per cycle in the EAG-corrected company base case

Table 33 Composition of BSC and concomitant medications (adapted from CS Table 65, Page 144 and executable model)

The model also considered the costs of concomitant medication for symptom management, which included analgesics, antibiotics, and anti-fungal drugs. The type and distribution of each medication applied in the model was based on treatment use in the BE HEARD I and II studies and is presented in Table 33. Some pack prices derived from the electronic market information tool (eMIT) differed from those applied in the executable model submitted by the company, the EAG has updated these prices in Table 33. This correction reduced per cycle concomitant therapy costs from £2.59 to £1.51. Note that the price of adalimumab, which comprises part of BSC in the company's base-case analysis, is also subject to confidential commercial arrangements. Pricing inclusive of all commercial arrangements available to the NHS is presented in a confidential appendix to this report.

Points for critique

Drug name	**Dosage**	**Dose/ unit**	**Pack size**	**CS pack price (£)**	**EAG pack price (£)**	**Unit cost source**	**% in receipt**
Ibuprofen	0.6 g /day	600 mg	84	£1.77	*£1.58*	eMIT (2023) [26]	13.72%
Paracetamol	4 g /day	500 mg	100	£2.80	*£0.84*	eMIT (2023) [26]	16.21%
Doxycycline 100 mg	100 mg x2 /day	100	1	£0.12	*£0.04*	NHSBSA (2023)[27]	7.95%
Metformin	500 mg x2 /day	250 mg	28	£0.33		eMIT (2023) [26]	6.16%
Omeprazole	20 mg /day	20 mg	28	£0.35		eMIT (2023) [26]	2.88%
Colecalciferol	800iu /day	800 units	30	£1.26		eMIT (2023) [26]	2.28%
Fluconazole	150 mg Q4W	150 mg	1	£0.35		eMIT (2023) [26]	5.96%
Amoxicillin	500 mg x3 /day	250 mg	21	£0.47		eMIT (2023) [26]	1.69%
Levonorgestrel	150 µg /day for 21 days	150 µg	63	£1.13		eMIT (2023) [26]	3.77%
Drospirenone; ethinylestradiol	3 mg /day for 21 days	3 mg	63	£5.67		eMIT (2023) [26]	1.49%
Levothyroxine sodium	100 µg /day	50 µg	28	£0.34		eMIT (2023) [26]	1.79%
Salbutamol	4 mg x 3.5 /day	100 µg	200	£1.40		eMIT (2023) [26]	2.68%
Total cost per cycle				*£2.59*	*£1.51*		
Adalimumab	160 mg on day 1, 80 mg day 15, then 40 mg QW from Week 4	40mg	40mg	£633.60		BNF	20.8%

As discussed in Sections 4.2.4 and 2.3, the EAG considers the inclusion of adalimumab as a component of BSC following discontinuation of bimekizumab or secukinumab to be inappropriate. Clinical advice to the company and EAG suggests instead that a proportion of patients may continue with their current treatment in the absence of alternative effective options when response has been partially lost. The EAG considers it very unlikely that these patients would reinitiate treatment with

adalimumab. The EAG therefore presents a scenario in Section 6.2 in which 20.8% of patients who switch to BSC following primary or secondary failure of bimekizumab or secukinumab continue to be treated with these agents alongside the usual combination of therapies comprising BSC.

The EAG noted that the company had interpreted Q4W secukinumab maintenance dosing as 'monthly', resulting in reduced acquisition costs for secukinumab. The EAG considers this to be an error in the company's interpretation of the licence for secukinumab and corrects this to one dose per model cycle for consistency with the accepted modelling approach in TA935. As discussed above, the EAG noted that several of the concomitant therapy costs included in the company model were misaligned with current eMIT values. These issues are considered model corrections and are incorporated into the corrected company base case presented in Section 6.

As discussed in Sections 4.2.2, 4.2.4, and 4.2.6.2, the EAG considers the company's approach to the application of stopping rules to have potentially significantly underestimated time on treatment, and thus treatment acquisition costs for bimekizumab and secukinumab. The EAG was unable to correctly implement stopping rules for active treatments in the time available but presents alternative simplistic approaches to exploring the implications of increasing treatment duration in the model in Section 6.2.

4.2.8.2 Health state unit costs and resource use

Healthcare resource use applied in the model was specific to the health state in which a patient resides. The company derived all estimates for the resource use required at each level of response defined by HiSCR directly from TA392 (via TA935), which derived these values from a physician survey. Modelled resource use relates primarily to hospitalisations due to HS, due to both surgery and unplanned management of wounds and other complications. The frequency of these events is assumed by the company to be independent of treatment received, despite the assumption that active therapy is associated with additional HRQoL benefits due to improved symptom management.

Given the addition of a higher response category than in the previous appraisals, the company fitted trend lines (polynomial degree 2 and logarithmic parametric) to resource use data across each level of response for each resource use item, to predict resource use at the HiSCR90 category. In each case, the company selected the model with the best fit according to the R^2 statistic. In the table below, the value for annual resource use predicted by the best fitting model for HiSCR90 response can be found in the rightmost column. In the submission, the company state that resource use frequency is 'adjusted to severity in BE HEARD I and II', with weightings provided in the company's clarification response.. Modelled annual resource use by response category is reproduced in Table 34

Table 34 Modelled annual resource use by health state based on TA392 (CS Table 66, Page 147)

Resource use item	Annual resource use by health state				
	Non-response	Partial response	Response	High response	Very high response
Hospitalisations for HS surgery	0.80	0.49	0.21	0.14	0.11
Outpatient visits due to HS surgery	0.92	0.63	0.35	0.23	0.17
Visits to wound care due to HS surgery	0.76	0.37	0.18	0.11	0.13
Hospitalisations, non-surgery related	0.46	0.27	0.21	0.13	0.11
Routine outpatient visits	4.67	4.38	3.51	3.17	2.83
Visits to wound care not due to HS surgery	0.45	0.66	0.52	0.68	0.70
A&E visits	0.58	0.45	0.21	0.14	0.07
Resource use item	**Annual resource use by health state**				
	Non-response	**Partial response**	**Response**	**High response**	**Very high response**
Hospitalisations for HS surgery	0.80	0.49	0.21	0.14	0.11
Outpatient visits due to HS surgery	0.92	0.63	0.35	0.23	0.17
Visits to wound care due to HS surgery	0.76	0.37	0.18	0.11	0.13
Hospitalisations, non-surgery related	0.46	0.27	0.21	0.13	0.11
Routine outpatient visits	4.67	4.38	3.51	3.17	2.83
Visits to wound care not due to HS surgery	0.45	0.66	0.52	0.68	0.70
A&E visits	0.58	0.45	0.21	0.14	0.07

, while unit costs for each item are presented in Table 35. Unit costs were derived from NHS Reference Costs.

Table 35 Modelled unit costs by resource use item (CS Table 67, Page 147)

Resource use item	Unit cost (£)	Comments
Hospitalisations for HS surgery	2,982.10	Weighted average: JC40Z (elective), JC41Z (elective), JC42C (elective), and JC43C (elective)
Outpatient visits due to HS surgery	152.30	Total outpatient attendance, HRG code: 330, total
Visits to wound care due to HS surgery	152.30	Total outpatient attendance, HRG code: 330, total
Hospitalisations, non-surgery related	1,654.30	Weighted average: JD07D (elective patients) and JD07K (elective patients)
Routine outpatient visits	152.30	Total outpatient attendance, HRG code: 330, total
Visits to wound care not due to HS surgery	152.30	Total outpatient attendance, HRG code: 330, total
A&E visits	278.10	Total HRGs, weighted average: VB01Z–VB09Z

Points for critique

As the health state cost and resource use estimates adopted by the company have been scrutinised and refined extensively in TA392 and TA935, the EAG is largely satisfied that they are an appropriate basis for decision making. However, the EAG are concerned that the unit cost for surgery-related hospitalisations may be too high, with an increase of over £500 compared with that accepted by the committee following validation by clinicians (£2,982 vs £2,402) in TA935. While the company stated that their costings were based directly on those accepted in TA935, in response to Clarification Question B13, the company confirmed that reference costs had been weighted according to the NHS activity per Healthcare Resource Group (HRG) code, rather than the distribution of surgery types (and settings of care) as accepted in TA392 and TA935. The EAG therefore explored the effect of replicating the accepted method used to derive average surgery costs in Section 6.2. The distribution and type of resource use comprising HS surgery accepted in TA392 and TA935 updated using current NHS Reference Costs, is presented in Table 36 below. In the opinion of clinical experts in these appraisals, the majority of surgeries would be undertaken on a day-case basis, with major elective skin procedures comprising a smaller proportion of surgeries on average. Applying previously accepted assumptions, the EAG calculates the average unit cost of surgery for HS to be £2,075.70. This difference arises largely from a significant proportion of surgeries being managed as day cases rather than as elective inpatient admissions.

Table 36 Comparison of surgery unit costing using TA935 approach with CS

Description	NHS ref. code	Setting of care	Cost	CS weight	TA935 weight
Multiple major skin procedures	JC40Z	Elective inpatient	£17,209.58	2.23%	0.00%
Major skin procedures	JC41Z	Elective inpatient	£8,724.08	13.3%	6.68%
Intermediate skin procedures	JC42C	Elective inpatient	£2,511.31	42.53%	13.16%
Intermediate skin procedures	JC42C	Non-elective short stay	£1,212.77	0%	13.16%
Intermediate skin procedures	JC42C	Day case	£1,496.78	0%	67.00%
Minor skin procedures	JC43C	Elective	£859.27	41.87%	0%
Total weighted CS unit cost	£2,982.10				
Total weighted unit cost based on TA935 approach	£2,075.70				

4.2.8.3 Adverse event unit costs and resource use

The company's base-case analysis did not include separate consideration of costs associated with management of adverse events, arguing that the AE profile of bimekizumab was similar to that of secukinumab, with the exception of oral candidiasis, and that AEs were not considered in the TA935 company model. The company presented a scenario analysis which included AE management costs, however, this did not appear to include a cost or event frequency for oral candidiasis infection.

Points for critique

The EAG notes that the cost and utility consequences of adverse events were included in the preferred set of assumptions on the EAG model in TA935, however, the committee did not express a position on this issue in the FDG. It is unclear why oral candidiasis was excluded from the modelled AEs in the scenario presented by the company, as this was specifically highlighted in the CS. The EAG acknowledges that AEs are likely to have a minimal impact on differential costs between bimekizumab and secukinumab but considers it appropriate to explore the effects of this scenario. Section 6.2 presents a scenario in which the cost of resolving oral candidiasis is included in the model, based on the frequency observed in the BE HEARD studies.

4.2.8.4 Confidential pricing arrangements

The EAG notes that there are a number of confidential commercial arrangements in place for drugs comprising the comparator regimen, and for drugs currently in use as subsequent treatment options. The treatment acquisition costs used in the analyses presented in the company submission and this report, include only the confidential pricing agreement for bimekizumab. Bimekizumab is currently available to the NHS with a [redacted]

Table 37 presents details of which comparator and subsequent treatments have confidential prices which differ from the publicly available list prices used to generate the results in this report. These prices were made available to the EAG and were used to replicate all analyses presented in this report for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices were correct as of 13th May 2024.

Table 37 Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of confidential arrangement
Bimekizumab	Simple PAS
Secukinumab	Simple PAS
Adalimumab (biosimilars)	Commercial Medicines Unit (CMU)

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

This section summarises the results of the company's updated base case as presented in the clarification response. The results presented in the following sections are inclusive only of the PAS discount for bimekizumab. Results inclusive of available commercial arrangements for the comparator treatments are provided in a confidential appendix to the EAG report.

5.1.1 Base-case results

In their response to clarification question B3, the company present their updated base-case analysis as a series pairwise ICERs, which compare bimekizumab against best supportive care and secukinumab. These results are reproduced in Table 38 below, alongside expected net health benefit at a threshold of £20,000 per QALY gained. These results suggest that bimekizumab is associated with a small increase in costs compared to secukinumab, and an increase in QALYs (QALY benefit of [redacted]). Bimekizumab is associated with a larger increase in costs and QALYs compared to BSC. The company's pairwise ICER versus secukinumab is £3,605 per QALY gained, and versus BSC is £12,444. For consistency with the NICE methods guide, the EAG also presents the results of the company's base case in a fully incremental format in Table 39.

Table 38 Company's deterministic base-case results (pairwise)

Technology	Total		Incremental		ICER	NHB @ 20k
	Costs	QALYs	Costs	QALYs		
Bimekizumab (vs)	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£3,605	0.35
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	£12,444	0.27

Table 39 Company's deterministic base-case results (fully incremental)

Technology	Total		Incremental		ICER	NHB @ 20k
	Costs	QALYs	Costs	QALYs		
Best Supportive Care	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated	-0.08
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£12,444	0.27

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analyses

The EAG requested several updates to the probabilistic analysis in the company's economic model at the clarification stage. The EAG asked that the company update the model to incorporate standard errors derived from the data source to sample probabilistic parameter values where possible, as in many cases the model assumed a standard error of 10% of the mean value. The EAG also requested that sampling of relative risks for each level of treatment response be performed jointly using the Convergence Diagnostic and Output Analysis (CODA) samples generated from the NMA, as the model sampled effect sizes for each treatment and level of HiSCR response independently. The probabilistic results of the company's updated base case (based on 1,000 model iterations) are reproduced in a pairwise (Table 40) and fully incremental format (Table 41) below. The total QALY gain in the probabilistic results differed markedly from that in the deterministic results, with incremental for bimekizumab versus secukinumab decreasing from [redacted] in the deterministic results to [redacted] in the probabilistic results. The source of this discrepancy was not identified by the EAG. Discrepancies can arise between probabilistic and deterministic results in complex Markov models, as they are inherently nonlinear. However, this may suggest a lack of robustness in the results to uncertainty in the model inputs.

Bimekizumab had an [redacted] probability of being the most cost-effective treatment option at a threshold of £20,000 per QALY in comparison to secukinumab, and [redacted] in comparison to best supportive care. The comparison between bimekizumab and BSC was subject to significant uncertainty, with a wide distribution of incremental costs and QALYs relative to the comparison with secukinumab, as illustrated in the cost-effectiveness plane (see Figure 11) The pairwise probabilistic ICER for bimekizumab versus secukinumab was £5,581 per QALY gained, and £18,313 per QALY gained versus BSC. Secukinumab was subject to extended dominance in the fully incremental analysis. The cost-effectiveness acceptability curve (CEAC) for the base-case analysis is presented in Figure 12.

Table 40 Company's probabilistic base-case results (pairwise)

Technology	Total		Incremental		ICER	NHB @ 20k
	Costs	QALYs	Costs	QALYs		
Bimekizumab (vs)	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£5,581	0.19
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	£18,313	0.04

Table 41 Company's probabilistic base-case results (fully incremental)

Technology	Total		Incremental		ICER	NHB @ 20k
	Costs	QALYs	Costs	QALYs		
Best Supportive Care	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.15
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£18,313	0.04

Figure 11 Company base-case cost-effectiveness plane for bimekizumab versus secukinumab

[redacted]

Figure 12 Company base-case CEAC for bimekizumab versus secukinumab and best supportive care (generated using company's executable model)

[redacted]

5.3 Company's additional scenario analyses

The company produced a range of scenario analyses in the original submission, which were updated along with their base case following their revision of all-cause discontinuation and the correction of its application in the executable model. The ICER for bimekizumab versus BSC ranged from £8,226 to £88,491, reflecting a scenario using TA392 health state utilities and using the NMA to derive BSC long-term transition probabilities respectively. Versus secukinumab, the ICER ranged between dominance and £48,159, reflecting the application of general population mortality rates across all health states, and using the NMA to derive BSC long-term transition probabilities respectively.

The EAG attempted to replicate the results presented by the company in Table 36 of the company's clarification response using the functionality built into the executable model. For a full description of each scenario, please refer to Table 75 of the CS. In several cases, these results did not align with those presented by the company. The EAG has therefore presented the pairwise results generated by the executable model for CS Scenarios 1 and 13 in Table 42 below. This table also presents the additional scenarios presented in response to the EAG's clarification questions, where model functionality has been provided by the company. CQ B7 could also not be fully replicated by the EAG, as utilities drawn from the CQ response tables were subject to rounding.

The EAG was unable to validate the company's scenario analyses as a model with full functionality to reproduce these analyses was not provided in time for integration into the EAG Report. It is therefore unclear whether the following results reflect the correct implementation of these scenarios. The results presented by the company for these scenarios can be found in the clarification response. Table 42 presents results replicated by the EAG using the executable model.

Table 42 Pairwise company updated scenario analysis results (clarification response scenarios)

Technology	Total		Incremental		ICER	NHB @ 20k
	Costs	QALYs	Costs	QALYs		
CS Scenario 1: Four response states, HiSCR90 merged with HiSCR75						
Bimekizumab (vs)	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£3,671	0.34
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	£12,550	0.27
CS Scenario 13: HiSCR90 resource use equal to HiSCR75						
Bimekizumab	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£3,652	0.35
Best Supportive Care	[redacted]	[redacted]	[redacted]	[redacted]	£12,468	0.27
CQ Scenario B2: SEC stopping rule in HiSCR<25 state = [redacted] to week 48						

Model functionality not provided						
CQ Scenario B4: All patients experience disease related mortality						
Bimekizumab	[redacted]					
Secukinumab					£1,272	0.27
Best Supportive Care					£14,127	0.15
CQ Scenario B5: Utility data pooled across treatments (not phase-specific)						
Bimekizumab	[redacted]					
Secukinumab					£4,166	0.29
Best Supportive Care					£14,629	0.16
CQ Scenario B6.1: Utility data pooled across treatments (phase-specific)						
Bimekizumab	[redacted]					
Secukinumab					£4,629	0.25
Best Supportive Care					£16,738	0.09
CQ Scenario B7: Use the same utility values for active treatment and BSC for HiSCR>75						
Bimekizumab	[redacted]					
Secukinumab					£3,411	0.37
Best Supportive Care					£11,782	0.31
CQ Scenario B16.1: Base-case results for biologic experienced patients						
Model functionality not provided						
CQ Scenario B16.2: Base-case results for biologic naive patients						
Model functionality not provided						

5.4 Model validation and face validity check

5.4.1 Validation undertaken by the company

The company state that the economic model was validated by an advisory board of clinicians practising in the English NHS and health economists. External technical validation was conducted via a NICE PRIMA review in 2023. Quality control was undertaken internally by company staff independent of the model development process, with validation including checks of model results, calculations, data references, the model interface, and VBA code. The company states also that the model calculations were verified by an independent agency.

5.4.2 Internal validation undertaken by EAG

As part of the EAG assessment of the economic analysis, the EAG performed high-level checks of the internal validity of the model and considered the face validity of the model's predictions. This included model calculation checks, including completion of the TECH-VER checklist to ensure results are consistent with inputs, and were robust to extreme values. The EAG identified no

significant structural errors in these checks, but a number of limitations in the model structure (e.g. associated with application of stopping rules) and errors in parameterisation (e.g. implementation of all-cause discontinuation probability – resolved in PFC B2). Where these issues remain relevant they are discussed in Section 4.

As a fully functional version of the company's updated executable model was not provided in sufficient time before the submission of the EAG Report, several of the scenarios presented by the company in their clarification response could not be validated.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified several serious limitations in the economic model presented by the company, which limited the extent to which the relative cost-effectiveness of bimekizumab and its comparators could be assessed and compared. These issues have been discussed in detail in Section 4. The following sections presents a number of scenario analyses in which the EAG considers alternative approaches and assumptions, in order to both demonstrate the flaws in the executable model presented by the company, and to explore alternative ways in which the value of bimekizumab could be assessed. A key uncertainty which could not be explored in the following sections was the application of subgroup analysis based on the biologic-experienced population, which the EAG has identified as being most relevant to the present decision problem. This was because a model containing the relevant functionality and input data was not provided in time to be considered in the EAG Report.

Descriptions of the EAG's exploratory analyses are provided in Section 6.1, and the degree of change on the ICERs and NHB compared to the company's base case is explored in Section 6.2. All results presented in Section 6.2 are replicated in the confidential appendix, inclusive of all confidential commercial arrangements available to NHS England.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted the following exploratory analyses after applying two corrections to the company's model. Firstly, a correction was made to the dosing frequency of secukinumab which the company had implemented on a monthly rather than a 4-weekly basis. The model was also corrected to include current eMIT prices provided by NHS England which differed from the company's in some instances. A comparison of the results of the company base-case analysis with and without the EAG's corrections is provided in Section 6.2. Each of the following scenario analyses are based upon the EAG-corrected version of the company's model.

The following scenarios include several of those already presented by the company in their scenario analyses (reported in the original CS) and those presented in response to requests by the EAG.

1. Exclude adalimumab costs and utilities from BSC.

As discussed in Sections 4.2.4 and 4.2.8, the EAG considered the company's inclusion of adalimumab as part of BSC to be potentially inappropriate, particularly given its large impact on total costs. Given the decision problem definitionally excludes adalimumab as a comparator (i.e., following failure or contraindication to adalimumab), it is unclear whether that 20.8% of patients on BSC should be modelled to receive adalimumab. This scenario explores the impact of removing adalimumab costs

and weighted utilities from BSC. This excludes adalimumab from BSC as both a comparator and a subsequent therapy.

2. A proportion of patients (20.8%) continue active therapy following loss of response instead of switching to adalimumab.

As discussed in Sections 4.2.4 and 4.2.8, the EAG consider it plausible that a proportion of patients may *continue* to receive a biologic therapy following partial loss of response but consider the re-initiation of a non-indicated therapy (i.e. adalimumab) to be unlikely. As a result, this scenario explores the impact of replacement of adalimumab in the post-discontinuation BSC treatment mix with bimekizumab or secukinumab in each treatment arm respectively.

3. Implement a 70-year time horizon.

As discussed in Section 4.2.5, the company adopted a 60-year time horizon to represent a lifetime time horizon in their base case. As noted by the EAG, at the end of the model time horizon, 1.37% of patients on bimekizumab remained alive, with a population age of 96.65. In scenarios relaxing the level of disease related mortality, up to 4% of patients remain alive at the end of the time horizon. This analysis implements a 70-year horizon to better capture lifetime costs and benefits of treatment.

4. Use transition probabilities based on loss of response in PIONEER II (linear fit) to represent the long-term effectiveness of BSC (Week 16+).

As discussed in Section 4.2.6, the EAG were concerned that the constraints applied on BSC transitions beyond Week 16 resulted in significant underestimates of the proportion of responders to BSC at any given time and failed to represent the natural history of HS. This scenario implements transition probabilities provided by the company based on a linear fit to loss of response data on placebo in PIONEER II for up to 36 weeks. These transitions were applied during the maintenance and post 48-week period (i.e., this scenario also removes the durable response assumption). As previously discussed, the EAG considers it likely that PIONEER II underestimates placebo outcomes in an NHS setting, as placebo responses may have improved with better availability of active therapies, and a much wider range of treatments are offered as part of BSC in NHS practice than were available to patients in PIONEER II. Furthermore, it is likely that for many patients at this line of therapy, a biologic may be included in the BSC treatment mix.

5. Use transition probabilities calculated based on the NMA to represent the long-term effectiveness of BSC (week 16+).

This scenario uses transition probabilities for BSC derived via the application of the RRs for placebo versus bimekizumab during the induction treatment phase in BE HEARD I and II to maintenance

phase transitions. This is consistent with the method used to derive secukinumab transition probabilities. These transition probabilities do not preclude transient improvement in symptoms over time, allowing patients to move freely between health states for the full model time horizon (i.e. the durable response assumption is also removed).

6. BSC maintenance phase transition probabilities applied to patients discontinuing active treatment (no durable response)

As described in detail in Section 4.2.6, non-responders who discontinue active treatment in the model are subject to initial treatment period transition probabilities for BSC, based on 16-week placebo response data from the BE HEARD studies. If a patient responds during this period, this response can be maintained indefinitely (through the application of the durable response assumption with no tunnel states to track time on BSC). This results in response rates of around [redacted] in the bimekizumab arm in perpetuity, despite >99% of patients having discontinued active treatment.

The EAG are concerned that the application of placebo response rates from the initial period of the trial may not represent the outcomes of patients in the NHS who discontinue active treatment. This scenario explores the use of maintenance period transition probabilities to model the outcomes of patients who discontinue active treatment, immediately from the point of discontinuation. In the basic implementation of this scenario, the 'gradual deterioration' assumption from the company's base-case analysis is applied. This scenario also excludes the 'durable response' assumption, which the EAG considers to have been improperly implemented.

7. Application of 12 weeks of active treatment costs to secondary non-responders following discontinuation.

As described in Sections 4.2.2 and 4.2.6.2, the EAG had concerns regarding the company's implementation of stopping rules for patients who discontinue following secondary loss of response. In the company's base case, patients immediately switch to BSC following loss of response. This results in the model very substantially underestimating the proportion of patients remaining on bimekizumab at Week 48.

It was established in TA935 that active treatment should only be discontinued when a patient stops responding and then maintains non-response for 12 weeks, following the addition of other treatments or surgery to re-establish response. This scenario explores the impact of simply adding 12 weeks of treatment costs to patients who discontinue treatment due to secondary non-response to establish a lower bound for total treatment acquisition costs. As patients cannot regain response and continue treatment, this scenario will underestimate total treatment costs. This scenario does not reflect QALY gain associated with continuing treatment.

8. Secondary non-response stopping rule of 20% per cycle in non-response health state.

As described in Sections 4.2.2 and 4.2.6, the EAG were concerned that in omitting the opportunity for patients to regain response in the model, i.e. because non-responders discontinue immediately, the rate of discontinuation on active treatment is significantly overestimated. The model predicts that around [redacted] of patients entering the maintenance phase with at least a partial response will have discontinued by Week 48. This compares to a value of [redacted]% over the equivalent period in the BE HEARD studies. This means a substantial component of the treatment effect, i.e., the ability to regain and maintain a response, is omitted from the model. The model is in this way unable to determine the relative effectiveness of treatment options.

In order to allow some patients to regain response and continue treatment during the maintenance phase, this scenario assumes that only 20% of patients in the non-response health state discontinue in any given cycle during the maintenance phase. This broadly reflects the probability of remaining in the non-response health state for three consecutive cycles on bimekizumab or secukinumab and provides a more accurate impression of costs and QALYs on active treatments.

9. Application of general population mortality to all patients regardless of response level.

As discussed in Section 4.2.6.3, the EAG had concerns with the company's base case assumption that only non-responders experience disease-related mortality. The EAG understands that excess mortality related to HS to be attributable to both acute sources (i.e. surgery) and long-standing metabolic and cardiovascular co-morbidities, which are not resolved immediately upon achieving a response to treatment.

This scenario demonstrates the effect of selective imposition of the SMR of 1.86 selected by the company on accrual of costs and QALYs in the model through implementing a general population mortality rate for all patients regardless of response states.

10. Application of disease-related mortality SMR of 1.86 to all patients regardless of response status.

This analysis applies the crude SMR of 1.86 (Lee *et al.)* as selected by the company to all patients regardless of response status.

11. Apply adjusted SMR of 1.48 reported by Lee *et al.* to all patients regardless of response status.

This scenario explored the impact of the *adjusted* SMR reported by Lee *et al.* rather than the *crude* SMR as applied in the company's base-case analysis for all patients regardless of response level.

12. Apply treatment-pooled, phase-specific utilities except for the non-response state for which applied utilities are both treatment- and phase-specific.

As discussed in Section 4.2.7, the company applied HRQoL data from BE HEARD II based on estimates of utility according to the treatment received, and to the treatment phase. The EAG were concerned that differences between the groups were not statistically significant differences, with some logically inconsistent values generated due to the small numbers of patients achieving higher levels of response to BSC.

This scenario explores the impact of a common (phase-specific) utility set across all treatment arms but applies treatment-specific utilities (i.e. biologics vs BSC) to the non-response health state, which appeared statistically significant and clinically plausible.

13. Application of utility values based on response category alone.

This scenario considers the application of HRQoL data pooled from all participants in the BE HEARD studies into a single value set based solely on response category, irrespective of both the intervention received and treatment phase. In this scenario, only response level determines the utility value applied.

14. Weight utilities by proportion receiving adalimumab in initial treatment period.

As discussed in Section 4.2.7, the company included adalimumab as a component of BSC, and as a result weighted utilities in the maintenance phase to reflect the additional benefit of biologics for the proportion of patients assumed to receive adalimumab. This weighting was not performed in the initial period of the model, which is inconsistent with the argument that patients treated with biologics will have improved HRQoL.

This scenario weights the utility applied to BSC patients in the initial treatment period in the same way as in the maintenance period.

15. Include oral candidiasis as adverse event based on trial-reported event rates.

As discussed in the EAG critique in Section 4.2.6.4 and 4.2.8, the company did not consider costs associated with the management of adverse events, arguing that the AE profile of bimekizumab was similar to that of secukinumab, with the exception of oral candidiasis. Despite this, the company's scenario including AEs did not include oral candidiasis, and it was not considered in the base case.

This scenario included the costs of managing oral candidiasis based on the frequency reported from the BE HEARD studies in the CS, applying the company's cost applied to 'Gastrointestinal Event'

and ‘Diarrhoea’ in their AE scenario, recognising that oral candidiasis is treated using relatively inexpensive over-the-counter medications.

16. Re-weight surgery costs as per TA935.

As discussed in Section 4.2.8, the EAG noted that the company’s method for deriving the unit cost for surgery-related hospitalisations was inconsistent with that accepted by the committee in TA935, which was based on a distribution of surgery types and care settings determined by extensive clinician feedback to the committee.

This scenario explores the weighting of surgery costs as per TA935. This approach results in a £2,076 unit cost applied to surgery-related hospitalisations, which was higher than the company base case value of £2,982.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 43 presents a comparison of the company’s base-case results following the update to their executable model submitted with their clarification response, and the company base case inclusive of corrections to secukinumab dosing and eMIT prices previously described. These results are presented in pairwise format. The effect of the EAG amendments is to increase the total costs associated with secukinumab, whilst reducing total costs on bimekizumab and BSC. This reduces the ICER of bimekizumab from £3,605 to £2,200 per QALY gained relative to secukinumab, and results in a much smaller reduction in the ICER versus BSC.

Table 43 EAG-corrected company base-case pairwise results (deterministic)

Technology	Total		Incremental		ICER	NHB @ 20k
	Costs	QALYs	Costs	QALYs		
Company base-case (post-clarification response)						
Bimekizumab (vs)	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£3,605	0.35
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	£12,444	0.27
EAG-corrected company base-case						
Bimekizumab (vs)	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£2,200	0.38
Best Supportive Care	[redacted]	[redacted]	[redacted]	[redacted]	£12,437	0.27

The results of the scenario analyses described in Section 6.1 are presented in Table 44 below. These results include the PAS discount for bimekizumab only. The exploratory scenarios presented in Table 44 are conducted on the EAG-corrected company base-case analysis, which includes the previously described amendment to secukinumab dosing and eMIT prices.

Results inclusive of all available PAS discounts and other commercial arrangements are provided in the confidential appendix to this report.

Table 44 EAG exploratory fully incremental scenario analyses (deterministic)

Scenario	Technology	Total		Incremental		ICER	NHB @ 20k
		Costs	QALYs	Costs	QALYs		
EAG-corrected company base-case	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.10
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£12,437	0.27
1. Exclude ADA from BSC (costs and utilities)	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.15
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£14,832	0.20
2. Replace ADA in BSC following discontinuation with 20.8% SEC/BKZ	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.01
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£8,644	0.41
3. 70-year time horizon	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.10
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£12,434	0.27
4. BSC long-term effectiveness - PIONEER linear fit (week 16+) (inc. no durable response)	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.40
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£50,543	-0.42
5. BSC long-term effectiveness - NMA adjusted (week 16+) (no durable response)	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.52
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£122,804	-0.68
6. BSC maintenance transition probabilities applied to discontinuing patients (no durable response)	Secukinumab	[redacted]	[redacted]				
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	SE ICER	0.62
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£249,940	-0.81
7. Apply 3 cycles active treatment	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.21

costs for secondary non-responders	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£16,067	0.14
8. SNR stopping rule of 20% per cycle in non-response HS	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£13,788	0.19
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£25,602	-0.08
9. General population mortality for all patients	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-0.13
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£12,176	0.34
10. Disease-related mortality for all patients (1.86)	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-0.16
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£14,127	0.30
11. Adjusted (1.48) SMR for all patients	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.14
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£13,287	0.20
12. Pooled phase-specific utilities (except NR)	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-0.10
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£10,897	0.39
13. Pooled utilities by treatment and phase	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.16
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£14,621	0.16
14. Weight utilities by proportion receiving ADA in initial treatment period	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.10
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£12,403	0.27
15. Including oral candidiasis cost based on trial frequency	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.10
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£12,445	0.27
16. Re-weight surgery costs as per TA935	BSC	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.15
	Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£15,347	0.17

6.3 EAG's preferred assumptions

The EAG presents two alternative combinations of the above scenarios in Table 45 and Table 46. This reflects two interpretations of the economic analysis submitted by the company. The first highlights the model assumptions the EAG have identified as either clinically implausible, or as artificially and selectively imposing treatment benefits for bimekizumab. This scenario essentially represents the benefit of bimekizumab perpetuated through the model from the trial-derived transition probabilities and HRQoL data alone, rather than interactions between discontinuation and assumptions relating to

BSC effectiveness. That is, this scenario demonstrates the extent to which the current model structure can capture the benefits of bimekizumab.

The second EAG base case analysis adopts a clinically plausible alternative set of assumptions which the EAG consider to more fairly represent the differential cost-effectiveness of secukinumab and bimekizumab in particular. The EAG considers this analysis more methodologically consistent both internally and with previous appraisals, and the most clinically plausible of the analyses presented. However, the EAG emphasises that it does not consider the model structure as presented to be appropriate for capturing the differential benefits of all treatment options, and absolute costs and QALYs, and those relative to BSC, are subject to a high degree of uncertainty. Important structural changes must be made before the model can be considered fit for decision making purposes.

The cumulative impact of the EAG's preferred assumptions on the EAG base-cases are presented in Table 45 and Table 46 below. There are commercial arrangements in place for the comparator treatments, which impact the magnitude and direction of the ICER effects across the scenario analyses below. Results inclusive of all available commercial arrangements are presented in the confidential appendix to this report.

As described above, the EAG adopts two base-case analyses which the EAG consider to be plausible interpretations of the economic analysis submitted by the company. These analyses incorporate the below assumptions in addition to the corrections described previously:

EAG base-case 1:

The EAG's first base-case incorporates the following assumptions:

- Scenario 2: Following discontinuation from active treatment (bimekizumab, secukinumab), replace adalimumab with discontinued active treatment.
- Scenario 3: Implement a 70-year time horizon.
- Scenario 5: Use transition probabilities calculated based on the NMA to represent the long-term effectiveness of BSC (Week 16+)
- Scenario 7: Apply 12 weeks of active treatment costs to secondary non-responders following discontinuation.
- Scenario 10: Disease-related mortality for all patients (SMR 1.86).
- Scenario 12: Apply treatment-pooled, phase-specific utilities except for the non-response state for which applied utilities are both treatment- and phase-specific.
- Scenario 14: Weight utilities by proportion receiving adalimumab in initial treatment period.
- Scenario 16: Re-weight surgery costs as per TA935.

EAG base-case 2:

- Scenario 2: Following discontinuation from active treatment (bimekizumab, secukinumab), replace adalimumab with discontinued active treatment.
- Scenario 3: Implement a 70-year time horizon.
- Scenario 5: Use transition probabilities calculated based on the NMA to represent the long-term effectiveness of BSC. (week 16+)
- Scenario 6: Apply BSC maintenance transition probabilities applied to patients discontinuing active treatments (incl. no durable response)
- Scenario 8: SNR stopping rule of 20% per cycle in non-response HS.
- Scenario 11: Apply adjusted SMR of 1.48 reported by Lee et al. to all patients regardless of response level.
- Scenario 12: Apply treatment-pooled, phase-specific utilities except for the non-response state for which applied utilities are both treatment- and phase-specific.
- Scenario 14: Weight utilities by proportion receiving adalimumab in initial treatment period.
- Scenario 15: Include oral candidiasis as adverse event based on trial-reported event rates.
- Scenario 16: Re-weight surgery costs as per TA935.

The cumulative impact of the EAG's preferred assumptions for each of the two presented EAG base cases are presented in Table 45 and Table 46 below.

Table 45 Cumulative effect of EAG's preferred model assumptions – deterministic (base-case 1)

Preferred assumption	Section in EAG report	Cum. ICER vs secukinumab	Cum. ICER vs best supportive care
Corrections to company base case	*6.1*	£2,200	£12,437
Scenario 2: Following discontinuation from active treatment (bimekizumab, secukinumab), replace adalimumab with discontinued active treatment.	*4.2.4, 6.1*	£79	£8,644
Scenario 3: Implement a 70-year time horizon.	*4.2.5, 6.1*	£94	£8,646
Scenario 5: Use transition probabilities calculated based on the NMA to represent the long-term effectiveness of BSC. (week 16+)	*4.2.6, 6.1*	£46,820	£102,160
Scenario 7: Apply 12 weeks of active treatment costs to secondary non-responders following discontinuation.	*4.2.2, 4.2.4, 6.1*	£51,535	£121,898
Scenario 10: Disease-related mortality for all patients (SMR 1.86).	*4.2.6.3, 6.1*	£53,933	£128,909

Scenario 12: Apply treatment-pooled, phase-specific utilities except for the non-response state for which applied utilities are both treatment- and phase-specific.	*4.2.7, 6.1*	£58,258	£144,352
Scenario 14: Weight utilities by proportion receiving adalimumab in initial treatment period.	*4.2.7, 6.1*	£58,169	£142,807
Scenario 16: Re-weight surgery costs as per TA935.	*4.2.8, 6.1*	£61,507	£145,930

Table 46 Cumulative effect of EAG's preferred model assumptions – deterministic (base-case 2)

Preferred assumption	Section in EAG report	Cum. ICER vs secukinumab	Cum. ICER vs best supportive care
Corrections to company base case	*6.1*	£2,200	£12,437
Scenario 2: Following discontinuation from active treatment (bimekizumab, secukinumab), replace adalimumab with discontinued active treatment.	*4.2.4, 6.1*	£79	£8,644
Scenario 3: Implement a 70-year time horizon.	*4.2.5, 6.1*	£94	£8,646
Scenario 5: Use transition probabilities calculated based on the NMA to represent the long-term effectiveness of BSC.	*4.2.6, 6.1*	£46,820	£102,160
Scenario 6: Apply BSC maintenance transition probabilities applied to patients discontinuing active treatments (incl. no durable response)	*4.2.6.1, 6.1*	£47,151	£114,602
Scenario 8: SNR stopping rule of 20% per cycle in non-response HS.	*4.2.6.2, 6.1*	£54,445	£102,882
Scenario 11: Apply adjusted SMR of 1.48 reported by Lee et al. to all patients regardless of response level.	*4.2.6.3, 6.1*	£55,906	£105,700
Scenario 12: Apply treatment-pooled, phase-specific utilities except for the non-response state for which applied utilities are both treatment- and phase-specific.	*4.2.7, 6.1*	£60,551	£120,836
Scenario 14: Weight utilities by proportion receiving adalimumab in initial treatment period.	*4.2.7, 6.1*	£60,664	£119,426
Scenario 15: Include oral candidiasis as adverse event based on trial-reported event rates.	*4.2.6.4, 6.1*	£60,731	£119,477
Scenario 16: Re-weight surgery costs as per TA935.	*4.2.8, 6.1*	£63,909	£122,330

The results of the EAG's (deterministic) base case analyses are presented in fully incremental format in Table 47 and pairwise in Table 48Table 50. Bimekizumab had a pairwise ICER of £61,507 per

QALY gained versus secukinumab in EAG base case 1, generating [redacted] incremental QALYs at an additional cost of [redacted]. The pairwise ICER for bimekizumab compared with secukinumab was £63,909 per QALY gained in EAG base case 2, with [redacted] additional QALYs generated, at an additional cost of [redacted].

Table 47 EAG base case 1 and 2: fully incremental results (deterministic)

Technology	Total		Incremental		ICER	NHB @ 20k
	Costs	QALYs	Costs	QALYs		
EAG base case 1						
BSC	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.55
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£145,930	-0.71
EAG base case 2						
BSC	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.63
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£122,330	-0.94

Table 48 EAG-corrected company base case 1 and 2: pairwise results (deterministic)

Technology	Total		Incremental		ICER	NHB @ 20k
	Costs	QALYs	Costs	QALYs		
EAG base case 1						
BSC	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£61,507	-0.16
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£145,930	-0.71
EAG base case 2						
BSC	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£63,909	-0.31
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£122,330	-0.94

6.4 Additional scenario analysis on the EAG's base case

To address remaining uncertainties, the EAG conducted an additional scenario on EAG base-case 2. As discussed elsewhere, use of PIONEER II data to represent BSC effectiveness likely represents a lower bound of the likely effectiveness of BSC in an NHS population. As a result, an additional scenario analysis is explored in Table 49, which compares the use of PIONEER II loss of response

data is employed instead of using the NMA and BE HEARD to model BSC outcomes in EAG base-case 2.

Table 49 Results of scenario analysis on the EAG alternative base case 2

	Technology	Total		Incremental		ICER	NHB @ 20k
		Costs	QALYs	Costs	QALYs		
EAG base case 2	Bimekizumab	[redacted]	[redacted]				
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£63,909	-0.31
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£122,330	-0.94
EAG base-case 2 - use of PIONEER instead of NMA to represent BSC effectiveness	Bimekizumab	[redacted]	[redacted]		[redacted]		
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£37,976	-0.19
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£267,323	-1.09

6.5 Probabilistic sensitivity analysis

The company used 1,000 model iterations to generate the probabilistic results in their submission. This did not appear to be sufficient to produce stable results on the EAG base case analyses, and so the PSA was run over 2,000 iterations to generate results for each of the EAG base case analyses. The results are shown in Table 50 for fully incremental results and Table 51 for the pairwise results. The corresponding cost-effectiveness planes and cost-effectiveness acceptability curves are shown in Figure 13 to Figure 16 below. Bimekizumab had a [redacted] probability of being the most cost-effective option at a threshold of £20,000 per QALY gained in EAG base case 1, and a [redacted] probability in EAG base case 2.

Table 50 EAG company base case 1 and 2: fully incremental results (probabilistic)

Technology	Total		Incremental		ICER	NHB @ 20k
	Costs	QALYs	Costs	QALYs		
EAG base case 1						
Best Supportive Care	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.54
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£156,712	-0.69
EAG base case 2						
Best Supportive Care	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	-0.66
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£125,980	-0.94

Table 51 EAG-corrected company base case 1 and 2: pairwise results (probabilistic)

Technology	Total		Incremental		ICER	NHB @ 20k
	Costs	QALYs	Costs	QALYs		
EAG base case 1						
Best Supportive Care	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£66,971	-0.15
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£156,712	-0.69
EAG base case 2						
Best Supportive Care	[redacted]	[redacted]				
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£60,637	-0.27
Bimekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£121,264	-0.92

Figure 13 EAG base-case 1: cost-effectiveness plane for bimekizumab versus secukinumab and best supportive care

[redacted]

Figure 14 EAG base-case 1: CEAC for bimekizumab versus secukinumab and best supportive care

Figure 15 EAG base-case 2: cost-effectiveness plane for bimekizumab versus secukinumab and best supportive care

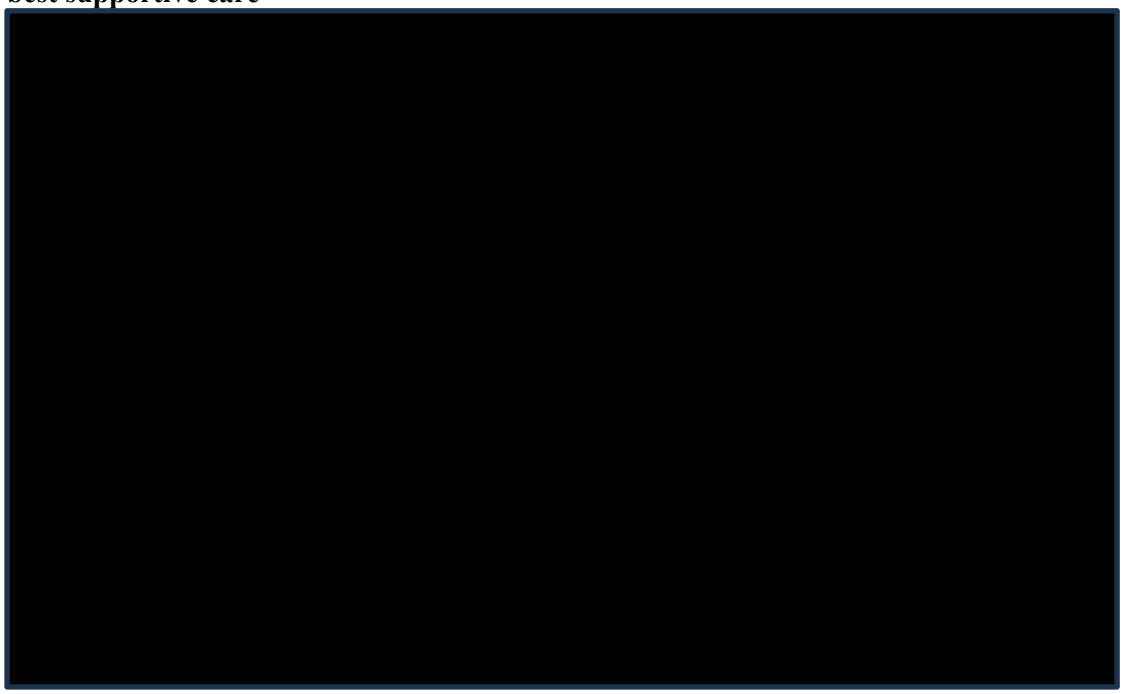


Figure 16 EAG base-case 2: cost-effectiveness plane for bimekizumab versus secukinumab and best supportive care

6.6 Conclusions of the cost effectiveness section

6.6.1 Summary of the company's cost-effectiveness analysis

The company developed a *de novo* Markov decision analytic model in Microsoft Excel to assess the cost-effectiveness of bimekizumab versus both secukinumab and best supportive care (BSC) for the treatment of adults with moderate-to-severe HS, for whom adalimumab is contraindicated or otherwise unsuitable. Effectiveness data from the BE HEARD I and II studies were compared with secukinumab and best supportive care through the use of an NMA, which informed transition probabilities between six health states defined by level of response (defined by HiSCR) and death.

The company's deterministic base-case analysis suggested that bimekizumab was both more costly and more effective than both secukinumab and best supportive care. Bimekizumab cost [redacted] and [redacted] more and generated [redacted] and [redacted] QALYs against secukinumab and BSC. This resulted in a pairwise ICER of £3,605 against secukinumab and a pairwise ICER of £12,444 against BSC. QALY gains on bimekizumab were driven primarily by a larger proportion of patients achieving a treatment response than on the other treatment arms. Due to a combination of assumptions applied in the model, this higher level of response was assumed to persist for the lifetime of patients treated with bimekizumab, though most patients were modelled to discontinue treatment within the first year.

In the company's probabilistic analysis, bimekizumab had the highest likelihood of being the most cost-effective treatment option at a threshold of £20,000 per QALY gained. The total QALY gain in the probabilistic results differed markedly from that in the deterministic results. This may be suggestive of a lack of model to parameter uncertainty.

Note that these results are based on the net price of bimekizumab inclusive of a patient access scheme but are exclusive of confidential commercial arrangements for other technologies included in the model.

6.6.2 Conclusions of the EAG's critique

The EAG's review of the company submission identified several areas of uncertainty, and a number of significant methodological issues. Where possible, the EAG has to address or illustrate the impact of these issues, but the EAG emphasises that it does not consider the present model structure able to capture the differential costs and benefits of each treatment option. The issues highlighted by the EAG are largely interconnected, and by simply removing the assumption of 'durable response' to BSC, the benefits of bimekizumab largely disappear. This is not because bimekizumab is an ineffective treatment, but because the primary mechanism of value generation in the model is not dependent on achieving a long-term response to bimekizumab. Instead, it is through achieving the maximum benefit of the 'durable response' assumption, whilst ensuring alternative treatment options get as little benefit from BSC as possible. Important structural changes which fully propagate the trial and synthesis results through the model must be made before the model can be considered fit for decision making purposes.

The EAG were concerned with the company's inclusion of adalimumab as a third-line treatment for patients who lose response to bimekizumab and secukinumab. The company's base case assumes that following discontinuation from active treatment, 20.8% of patients go on to receive adalimumab as part of BSC. This use of adalimumab is not recommended by NICE and to the EAG's knowledge, is not funded by the NHS. Clinical advice to the company and EAG suggests it is plausible that a proportion of patients may instead continue to receive their current biological therapy following a partial loss of response. The EAG prefers to assume that a proportion of patients who may still be experiencing some treatment response below the HiSCR25 threshold would continue on their current treatment (i.e. bimekizumab or secukinumab) rather than switching to adalimumab.

A key area of uncertainty relates to the mismatch in the composition of the modelled population with that considered in the decision problem for the present appraisal. The EAG considered the biologic-experienced population most relevant at this line of therapy, as definitionally, almost all patients will have previously been treated with adalimumab. This substantially reduces the size of the population for whom efficacy data is available from the BE HEARD studies. Whilst efficacy estimates appeared numerically similar between the whole trial population and this subgroup, they were subject to a great deal additional uncertainty. The EAG requested that these results be integrated into the executable model in order to generate cost-effectiveness results for this relevant population. However, a model

was not provided in time for integration into the EAG Report. This remains a substantial area of uncertainty.

There remains uncertainty regarding the cost- and clinical-effectiveness of up-titration of secukinumab, in alignment with the product's marketing authorisation. This allows for the standard Q4W maintenance dose to be increased to Q2W for an additional 12 weeks in patients who do not achieve a response at 16 weeks and is likely to comprise part of NHS practice. This may mean that the modelled outcomes for secukinumab may underrepresent the effectiveness of secukinumab in an NHS setting, though there is limited direct evidence on the effectiveness of this strategy. The EAG considers this an unresolved uncertainty, and the net effect upon its cost-effectiveness is uncertain.

One of the primary areas of uncertainty relates to company's approach to modelling stopping rules. Firstly, the company assumed that patients on bimekizumab and secukinumab who lost response during maintenance treatment (secondary non-responders) discontinued treatment immediately. The committee in TA935 accepted that treatment should only be discontinued when a patient stops responding and maintains non-response for 12 weeks, typically following additional treatment and/or surgery to re-establish response. The effect of this assumption was to substantially overestimate the proportion of patients discontinuing active treatment compared to the BE HEARD studies. This assumption means the model fails to capture a significant component of the treatment effect (i.e., the ability to regain and maintain a treatment response) and the costs associated with the continuation of treatment. Whilst the EAG has implemented some simple scenarios to illustrate the potential impact of this assumption, the model at present cannot determine the relative effectiveness of alternative treatment options without structural modifications.

A related issue identified by the EAG was the interaction between the company's preferred 'durable response' assumption with BSC efficacy assumptions, and the company's application of discontinuation. As patients on BSC are assumed to remain in their current health state indefinitely after Week 48, patients discontinuing active treatment can equally retain their level of response indefinitely. This impacts both patients who discontinue for 'other reasons' and patients who discontinue due to non-response, as the latter group of patients can achieve a response to BSC upon switching, which is then maintained indefinitely (depending on how close to model Week 48 discontinuation occurs). The model based the first 12 weeks of transitions following discontinuation of active treatment on placebo response rates from the BE HEARD studies. This results in response rates of ~[redacted] in perpetuity on bimekizumab, compared to [redacted] on BSC, despite >99% of patients having discontinued treatment. This combination of assumptions generates around 75% the incremental benefits of bimekizumab. Associating a loss of response to active treatment with a substantial boost to response rates may be inappropriate. A significant component of placebo response in a trial setting is a patient's belief that they are may be receiving an effective therapy as well as

regression to the mean. As patients who are unblinded to the fact they have stopped receiving active treatment are unlikely to experience a placebo response beyond the cycles of exacerbation and improvement inherent to HS and its management, the EAG considered it appropriate to apply maintenance phase BSC outcomes to these patients from the point of discontinuation.

The modelling of outcomes on BSC is also subject to a high level of uncertainty. These issues include both BSC as a comparator, but also for patients discontinuing active therapies who transitioned onto BSC. Another issue highlighted by the EAG relates to the constraints imposed on BSC maintenance phase transition probabilities. The company's base case only allows patients to continue in their current health state or to experience decline. The EAG consider this to be an incomplete representation of the natural history of HS, which is characterised by periods of exacerbation and transient improvements. This is an incomplete representation of the natural history of HS, which is a condition characterised by transient exacerbations and improvements induced by treatment and surgery. This resulted in a proportion of patients with a >HiSCR50 response at Week 36 of [redacted] in the model, compared to 15.9% in PIONEER II (which likely underrepresents response to NHS BSC), and [redacted] predicted using the NMA to adjust bimekizumab transition probabilities. The EAG preferred that BSC transition probabilities be sourced from the NMA across both the initial and maintenance treatment periods for consistency with secukinumab.

The company base case applied a standardised mortality ratio (SMR) of 1.86 to patients only in the non-response health state while all other patients experience general population mortality. It is the EAG's understanding that excess mortality experienced by HS patients relates to both acute sources (i.e., surgery) and long-standing metabolic and cardiovascular co-morbidities, which are not resolved immediately upon achieving a response to treatment. It is unclear whether it is appropriate for patients in response health states to be exempt from disease-related mortality. The EAG explored the impact of this assumption on cost-effectiveness estimates but further input on the relationship between duration of response and reduction in the burden of co-morbidities in HS may inform a more sophisticated and realistic implementation of mortality.

The company's approach to weighted surgery costings appeared to be inconsistent with the approach taken in TA935. The unit cost for surgery-related hospitalisations was weighted by NHS activity per HRG code, rather than according to the distribution of surgery types and settings of care established by the committee in TA935. This re-weighting resulted in a unit cost increase of over £900 compared to using the TA935 method. The EAG included the reweighted value in each of the preferred base-case analyses and consider this issue resolved.

The impact of these uncertainties was considered in a series of exploratory analyses. The individual assumptions with the largest impact upon the cost-effectiveness of bimekizumab related to alternative approaches to modelling the efficacy of BSC and the removal of the ‘durable response’ assumption.

7 SEVERITY MODIFIER

The company stated that they did not consider the technology to meet the criteria for a severity modifier.

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APPENDICES

APPENDIX 1: Summary of results from BE HEARD trials

The imputed results from the HS-ABX analyses for the whole BE HEARD cohort (both biologic-naïve and biologic-experienced patients) are provided below.

Table 52 Results of the BE HEARD trials at 16 weeks for overall (predominantly biologic-naïve) cohort

NICE scope outcome	Trial outcome	Pooled or individual trial result	Bimekizumab Q2W/Q2W	Bimekizumab Q2W/Q4W	Placebo
Disease progression	No data collected in trial				
Inflammation and fibrosis	No data collected in trial				
Clinical Response	HiSCR50, % (95% CI) [n]	BH I	59.8 (51.4, 68.2) [143]	50.4 (42.1, 58.8) [146]	34.0 (23.0, 45.1) [72]
	HiSCR50, % (95% CI) [n]	BH II	56.1 (47.9, 64.4) [145]	61.1 (52.9, 69.2) [146]	32.3 (21.5, 43.1) [74]
	HiSCR75, % (95% CI) [n]	BH I	39.9 (31.6, 48.3) [143]	37.4 (29.4, 45.5) [146]	18.3 (9.3, 27.3) [72]
	HiSCR75, % (95% CI) [n]	BH II	38.8 (30.7, 46.9) [145]	40.5 (32.3, 48.7) [146]	15.7 (7.2, 24.1) [74]
	HiSCR25, % (95% CI) [n]	Pooled	[redacted] [288]	[redacted] [292]	[redacted] [146]
	HiSCR90, % (95% CI) [n]	Pooled	21.0 (16.1, 25.8) [288]	22.0 (17.2, 26.9) [292]	8.5 (3.9, 13.1) [146]
	HiSCR100, % (95% CI) [n]	Pooled	15.6 (11.2, 19.9) [288]	16.6 (12.2, 21.1) [292]	5.6 (1.8, 9.4) [146]
Disease severity	AN count percentage change from baseline (SE) [n]	Pooled	−54.2 (3.8) [288]	−53.8 (3.1) [292]	−28.2 (4.8) [146]
	Reduction in DT count, LS mean change (95% CI) [n]	Pooled	−1.45 (−1.76, −1.15) [580]		−0.37 (−0.85, 0.11) [146]
	Proportion with ≥5 DTs at baseline achieving ≥ 3 DT reduction, % (95% CI) [n]	Pooled	61.6 (56.1, 67.2) [101]	61.0 (54.6–, 67.5) [76]	30.5 (16.7, 44.4) [43]
	Proportion with IHS4 ‘mild’ rating (%) [n] [none ‘mild’ at baseline in any group]	Pooled	No data presented	24.6 [292]	15.3[146]
	Proportion with IHS4-55 response % (95% CI) [n]	Pooled	53.1 (47.1, 59.0) [288]	53.5 (47.7, 59.4) [292]	26.2 (19.0, 33.5) [146]
	Proportion of patients with flare at 16 weeks, % (95% CI) [n]	BH I	15.2 (9.0, 21.4) [143]	22.6 (15.6, 29.6) [146]	39.5 (28.1, 50.9) [72]
	Flare at any time during initial treatment period, % (95% CI) [n]	BH II	21.4 (14.6, 28.2) [145]	19.0 (12.5, 25.6) [146]	25.2 (15.1, 35.2) [74]
Discomfort and pain	Change from baseline in worst skin pain NRS (SE) [n]	BH I	−1.98 (0.18) [289]		−0.92 (0.32) [72]
	Change from baseline in worst skin pain NRS, % (SE) [n]	BH II	−1.87 (0.16) [291]		−0.45 (0.30) [74]

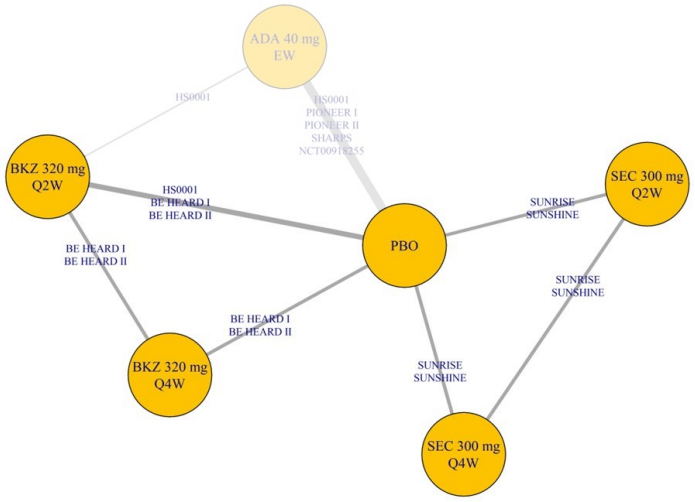
NICE scope outcome	Trial outcome	Pooled or individual trial result	Bimekizumab Q2W/Q2W	Bimekizumab Q2W/Q4W	Placebo
	HSSDD worst skin pain NRS response (95% CI) [n]	BH I	36.7 (29.4, 44.1) [289]		16.1 (4.5, 27.8) [72]
	HSSDD worst skin pain NRS response (95% CI) [n]	BH II	36.7 (29.8, 43.6) [291]		11.1 (1.8, 20.4) [74]
	Proportion with NRS30 response % (95% CI) [n]	Pooled	49.9 (44.7, 55.0) [399]		26.9 (17.1, 36.7) [95]
	Proportion with HSSQ 0 skin response % (95% CI) [n]	Pooled	10.8 (8.6, 12.9) [not reported]	7.1 (5.3, 8.9) [not reported]	2.3 (0.0, 4.8) [not reported]
Health-related quality of life	Mean change from baseline in DLQI mean (SE) [n]	BH I	−5.6 (0.5) [143]	−4.3 (0.5) [146]	−2.9 (0.8) [72]
	Mean change from baseline in DLQI mean (SE) [n]	BH II	−5.0 (0.5) [145]	−4.2 (0.5) [146]	−3.2 (0.6) [74]
	DLQI MCID response % (95% CI) [n]	Pooled	56.5 (52.0, 60.9) [496]		45.9 (37.0, 54.9) [125]
	HiSQOL total change from baseline, mean (SE) [n]	Pooled	−11.0 (0.4) [868] (includes Q4W data)		−5.8 (0.9) [146]
	HiSQOL symptoms domain change from baseline, mean (SE) [n]	Pooled	−2.6 (0.1) [868] (includes Q4W data)		−1.4 (0.3) [146]
	HiSQOL psychological domain change from baseline, mean (SE) [n]	Pooled	−2.3 (0.1) [868] (includes Q4W data)		−1.4 (0.3) [146]
	HiSQOL activities-adaptation domain change from baseline, mean (SE) [n]	Pooled	−6.0 (0.2) [868] (includes Q4W data)		−3.1 (0.5) [146]

AN, abscess and inflammatory nodule; BH, BE HEARD; CI, confidence intervals; DLQI, Dermatology Life Quality Index; DT, draining tunnel; EQ-5D-3L, 3-level, 5-dimension EuroQol questionnaire; HiSCR, Hidradenitis Suppurativa Clinical Response; HiSQOL, Hidradenitis Suppurativa Quality of Life; HS, hidradenitis suppurativa; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary; HSSQ, Hidradenitis Suppurativa Symptom Questionnaire; IHS4, International Hidradenitis Suppurativa Severity Score System; IHS4-55, 55% reduction in IHS4 total score; MCID, minimal clinically important difference; NICE, National Institute for Health and Care Excellence; NRS, numerical rating scale.
Note that for weeks 0-16, the bimekizumab Q2W/Q4W and bimekizumab Q2W/Q2W groups would have received identical treatments, both receiving Q2W only during this period. Therefore, both groups represent the same Q2W treatment for this period, and so pooled data from both bimekizumab Q2W/Q4W and bimekizumab Q2W/Q2W groups are presented where possible. If data are presented for each of the bimekizumab Q2W/Q4W and bimekizumab Q2W/Q2W groups separately, this is because no pooled data were presented in the CS.

APPENDIX 2: Summary of NMA and MAIC results

The NMA for 0-16 weeks (12 weeks for adalimumab trials) using all trial data (biologic naïve and biologic experienced) was set up according to the network diagram in Figure 17, involving 9 trials. Its results are summarised in Table 53. The results from the corresponding MAICs using all trial data are shown in Table 54.

Figure 17 NMA evidence network at weeks 12–16 (Figure 19, CS)



Adalimumab is greyed out in the evidence network as, although these trials were included in the NMA when relevant outcome data were reported, a comparison with adalimumab is not considered within scope.

Table 53 Week 16 NMA results using full trial populations

	BKZ Q2W vs SEC 300 mg Q2W	BKZ Q2W vs SEC 300 mg Q4W
HiSCR50[OR (95% CrI)]*	1.70 (1.16, 2.45)	1.69 (1.14, 2.43)
HiSCR75[OR (95% CrI)]*	2.02 (1.38, 3.20)	1.85 (1.26, 2.90)
HiSCR90[OR (95% CrI)]*	1.86 (1.30, 2.75)	1.62 (1.13, 2.36)
HiSCR100[OR (95% CrI)]*	1.77 (1.12, 2.77)	1.88 (1.18, 3.00)
IHS4-55 [OR (95% CrI)]	1.96 (1.22, 3.17)	1.91 (1.18, 3.06)
IHS4 CfB [MD (95% CrI)]	−4.35 (−8.53, −0.17)	−6.45 (−10.55, −2.27)
% change from baseline in AN count [MD (95% CrI)]	−6.71 (-19.90, 6.48)	−6.56 (−19.85, 6.80)
Absolute change from baseline in draining tunnel count [MD (95% CrI)]	−0.74 (−1.58, 0.09)	−1.14 (−1.97, −0.34)
Skin pain response (NRS30) [OR (95% CrI)]	1.51 (0.80, 2.85)	1.75 (0.93, 3.32)

AN, abscess and inflammatory nodule; BKZ, bimekizumab; CfB, change from baseline; CrI, credible intervals; HiSCR, Hidradenitis Suppurativa Clinical Response; IHS4, International Hidradenitis Suppurativa Severity Score System; IHS4-55, 55% reduction in IHS4 total score; MD, mean difference; NRS, numerical rating scale; OR, odds ratio; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab.
*Placebo adjustment applied

Table 54 Results of MAICs for HiSCR outcomes using full trial populations

HiSCR outcome	**Odds ratio (95% CI) when bimekizumab is compared to:**	
	Secukinumab 300 mg Q2W	**Secukinumab 300 mg Q4W**
HiSCR50	2.00 (1.42, 2.80)	2.06 (1.45, 2.92)
HiSCR75	1.91 (1.35, 2.70)	2.13 (1.49, 3.05)
HiSCR90	2.05 (1.39, 3.04)	2.04 (1.36, 3.04)

CI, confidence intervals; HiSCR, Hidradenitis Suppurativa Clinical Response; Q2W, every 2 weeks; Q4W, every 4 weeks.

Single Technology Appraisal

Bimekizumab for treating moderate to severe hidradenitis suppurativa [ID6134]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 9 July 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Incorrect source of secukinumab stopping rule in table on page 17

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17 (Issue 5 table) states: "*The marketing authorisation for secukinumab allows for the standard Q4W maintenance dose to be increased to Q2W for an additional 12 weeks in patients who do not achieve a response at Week 16*"	Clarify that stopping rule for secukinumab was derived by NICE rather than detailed in the marketing authorisation.	The stopping rule of additional 12 weeks was derived by NICE - it is not within the wording of the marketing authorisation.	We have removed the reference to an "additional 12 weeks".

Issue 2 Use of NMA for BSC transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19 (Issue 7 table) states that *"The EAG prefers a model structure which allow patients to transition freely between health states indefinitely on BSC, and thus treatment efficacy is less dependent upon BSC assumptions."*	The EAG prefers a model structure which allow patients to transition freely between health states indefinitely on BSC.	The use of the NMA-derived risk ratios for the BSC transition probabilities is also an influential assumption. It assumes that the placebo effect is maintained, while removing placebo effect from active therapies.	Not a factual error. This statement refers to the removal of the 'durable response' assumption for BSC, and the effect of this assumption alone (in

			combination with any other) on the efficacy of bimekizumab and secukinumab.

Issue 3 Impact of bimekizumab on long-term response in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 23 states the primary method of value generation in the model is through *"maximising benefit derived from the 'durable response' assumption whilst ensuring the comparators receive minimal benefit from BSC."*	The text needs to be revised to explain the comparison: bimekizumab vs BSC or vs secukinumab	The difference between bimekizumab and secukinumab is driven by secukinumab having lower rates of initial response and therefore a greater propensity to lose response over time.	Not a factual error. This point refers to the fact that differences between BKZ and SEC are not driven by response rate alone, but rather the interaction of discontinuation and BSC assumptions.

Issue 4 Inclusion of timepoint (week 12) for some NMAs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 35 (Section 3.1.5) the EAG notes that an NMA was conducted to estimate the relative efficacy of bimekizumab, secukinumab and placebo at week 16.	Suggest editing wording to: "The company conducted a network meta-analysis (NMA) to estimate the relative efficacy of bimekizumab, secukinumab and placebo at week 12/16,..."	Week 12 timepoints were included in some NMAs (e.g. adalimumab studies informed baseline risk and these were generally reported at week 12, and HS0001 also reported data at week 12).	Thank you – this has been amended.

Issue 5 Inclusion of timepoint for primary outcome of BE HEARD trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 37 HiSCR50 is described as the primary outcome of the BE HEARD trials, without any mention of timepoint at which this outcome was assessed.	Suggest rewording to: "HiSCR50 at week 16 was the primary outcome, all others were secondary outcomes."	The primary outcome was proportion of patients with HiSCR50 at week 16.	Not a factual inaccuracy. We note that HiSCR50 is considered at several time points in BE HEARD and this assessment.

Issue 6 Definition of intercurrent events related to antibiotic use

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 40 the definition for intercurrent events includes discontinuation due to antibiotic use for any reason, without differentiating between stable antibiotic use (which was allowed) and newly initiated antibiotic use.	Suggest rewording to: "Intercurrent events were originally defined as discontinuation due to lack of efficacy, discontinuation due to adverse events and antibiotic use for any reason (if this antibiotic use was newly initiated on or after the baseline visit)".	Stable antibiotic use (i.e. if the patient had been on antibiotics for at least 28 days before baseline) was permitted and did not count as an intercurrent event. Table 13 (p. 57) and section 2.3.14 in Document B of the CS provide the definition of intercurrent events.	Thank you – this has been amended.

Issue 7 Definition of flare outcome at week 16 of BE HEARD trials (for pooled population, biologic-experienced subgroup)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 9 on page 45 defines the flare outcome of the BE HEARD trials at week 16 as "*flare at any time during initial treatment period*".	These data relate to flares at week 16, not at any point during the first 16 weeks. These data were presented in Table 14 of the clarification question responses as "Proportion of patients with flare at 16 weeks in the pooled BE HEARD population biologic-experienced subgroup". Suggest this	Incorrect to state this outcome is inclusive of entire initial treatment period rather than the proportion of patients with flare at week 16 (specific timepoint).	Thank you – this has been amended.

	same wording (i.e., “Proportion of patients with flare at 16 weeks”) is used here.		

Issue 8 Proportion of patients in placebo group experiencing hidradenitis at week 16

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 48 the proportion of patients experiencing hidradenitis in the placebo group is listed as 10%	Change of value to 10.3%.	We believe this should be 10.3% to align with the value presented in Table 49 of Document B and as all other values in the paragraph are given to one decimal place.	Thank you – this has been amended.

Issue 9 NMA timepoints and data clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49 (Section 3.8) states: “*An NMA was carried out using the 0–16-week data, but because data after 16 weeks were not placebo controlled an unanchored MAIC was*	We believe this should read: “An NMA was carried out using the 16-week data from the BE HEARD trials and 12/16-week data from comparator trials. As the bimekizumab and secukinumab trials after 16 weeks were not placebo controlled, an unanchored MAIC was necessary to compare bimekizumab at	NMAs were conducted at specific timepoints (12 weeks and 16 weeks) rather than over treatment periods (0-16 weeks), and week 48 bimekizumab data were compared to week 52 secukinumab data.	Not a factual inaccuracy, but we have amended for clarity.

necessary for the 16-48 week data."	48 weeks to secukinumab at 52 weeks."		

Issue 10 Inclusion of biologic-experienced patients in the NMA and MAIC analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49 states: "*The original NMA and MAIC analyses included patients who were biologic-naïve."* *Page 53 states: "The HiSCR analyses in the biologic-naïve populations involved a post hoc placebo-adjustment using a meta-regression model in the overall analysis."*	The term "primarily biologic-naïve" should be used throughout.	Both patients who were biologic naïve and biologic experienced were included in the original NMA and MAIC analyses of the overall population. Referring to the population as "biologic naïve" could imply that biologic-experienced patients were excluded, which is not correct.	Not typically a factual inaccuracy. We stated that biologic-naive patients were included to clarify that the sample is not the preferred biologic-experienced group: we are not implying that only biologic-naïve patients were evaluated. We have made amendments where required for clarity.

Issue 11 Typo regarding treatments in biologic-experienced NMAs (Section 3.8)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49 reads: "*Four randomised trials were identified that involved biologic-experienced participants, covering adalimumab, bimekizumab, secukinumab and placebo"*	This is a typo and should not include adalimumab. This sentence should read: "Four randomised trials were identified that involved biologic-experienced participants, covering bimekizumab, secukinumab and placebo"	The biologic-experienced NMAs only covered bimekizumab, secukinumab and placebo.	Thank you – this has been amended.

Issue 12 Incorrect table reference (Section 3.8)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 50, the table reference is incorrect ("*Fuller results are given in Table 27 of the company response to clarification.*")	Correction of typo from "Table 27" to "Table 28."	Biologic-experienced subgroup baseline characteristics are presented in Table 28 of the company response to clarification.	Thank you – this has been amended.

Issue 13 Number of trials informed model selection decision making (Section 3.8)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 53 states: "*Fixed effect models were used for all analyses because the Deviation Information Criterion (DIC) in the fixed effect model was no more than 5 points above the random effects model.*"	Suggest rewording to "Fixed effect models were used for all analyses because the Deviation Information Criterion (DIC) in the fixed effect model was no more than 5 points above the random effects model and the networks generally contained a sparse number of trials."	As mentioned in clarification question response A21 ("Given the sparse number of trials in the network and DIC results, the fixed-effect model was preferred") both the DIC and sparse number of trials informed model selection.	Thank you – this has been amended.

Issue 14 Confidence vs credible intervals (Section 3.9.2.1 and Section 3.9.2.3)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 54 (Section 3.9.2.1) states: "*The point estimates also indicated a benefit over both doses of secukinumab, but confidence intervals were wide due to the small sample sizes."* *"These results have similar estimates to those in the analysis of biologic-experienced patients, but with*	Correction to credible intervals (rather than confidence intervals) throughout.	As Bayesian NMAs were conducted, credible intervals instead of confidence intervals were generated.	Thank you – these errors have been amended.

narrower confidence intervals due to the larger sample sizes (see also Appendix 1).” Page 56 (Section 3.9.2.3) states: *“However, the confidence intervals were wide for all analyses, indicating high levels of uncertainty/imprecision.”*			

Issue 15 Typo of IHS4-55 (Section 3.9.2.2)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 55 states: “*For HIS4-55 and percentage change in AN count”*	This should read “IHS4-55”.	Typo.	Thank you – this has been amended.

Issue 16 Inclusion of 52 weeks in timepoint for MAIC (Section 3.10.1)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 58 (Section 3.10.1) states: *“For the follow-up time of 48 weeks the CS presented a Matched Adjusted Indirect*	This should read 48/52 weeks throughout.	The MAIC included 48-week bimekizumab data and 52-week secukinumab data.	Thank you, we have clarified this point.

Comparison (MAIC) analysis to compare bimekizumab to secukinumab." *"The choice of trials and trial arms was appropriate, and the EAG agrees that it is reasonable to only compare bimekizumab to secukinumab at 48 weeks."*			

Issue 17 Reasons for not adjusting the MAIC for abscess and inflammatory nodules count (Section 3.10.1)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 58 states the MAIC was *"not adjusted for components of the abscess and inflammatory nodules count, because of the complexity of doing this"*	Suggest the following edit: "not adjusted for components of the abscess and inflammatory nodules count, due to the collinearity between these variables and the combined AN count"	These components were not adjusted for not due to complexity but instead due to collinearity as AN count is a composite of both abscess count and inflammatory nodule count.	We have amended for clarity.

Issue 18 MAIC analysis set (Section 3.10.1)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 58 states: "*Patients who received antibiotics were treated as non-responders to treatment only if antibiotics were given as a rescue treatment. This was in line with the analysis performed in the trials of secukinumab.*"	Suggest removing these two sentences.	MAIC did not use mNRI (HS-ABX) as the secukinumab trial publications only report observed data in maintenance. Instead, NRI was calculated from the observed cases.	We have amended this sentence to clarify that it refers only to the BE HEARD trials.

Issue 19 Validity of MAIC results (Section 3.10.2 and Section 3.12)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 59 it is stated that "*The EAG considers it highly implausible that perfect matching can be achieved in a MAIC across 12 factors and both secukinumab arms*." It is also stated on page 61 that the adjusted data were implausibly similar.	Suggest removing wording that results are implausible.	The analysis was conducted in line with NICE DSU 18 and was checked internally. Additionally, analysis code was provided during clarification.	Not a factual inaccuracy.

Issue 20 Incorrect value for upper bound of CI for odds ratio for HiSCR75 outcome (Table 18)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 59 (Table 18), the upper bound of the 95% CI for secukinumab 300 mg Q2W for the HiSCR75 outcome reads 2.80.	This should read 2.70.	Typo.	Thank you, this has been corrected.

Issue 21 Inclusion of patients with prior exposure to adalimumab in the BE HEARD trials (Section 3.12)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 60 reads as though no patients in the trials had prior exposure to adalimumab ("*Most patients in the trials had no prior exposure to adalimumab (they were biologic-naïve); a small number had exposure to prior biologic therapies other than adalimumab*")	Change to mention that some patients in the BE HEARD trials did have prior exposure to adalimumab. Suggested wording: "Most patients in the trials had no prior exposure to adalimumab (they were biologic-naïve). In response to clarification the company provided data on prior biologic experience in the BE HEARD trials in Table 3 and Table 4. In the pooled BE HEARD trial populations 17.3% of patients had prior adalimumab exposure, which represents 91.1% (174 of 191) of	Some patients in the BE HEARD trials did have prior exposure to adalimumab, we believe this should be reported here.	Text has been amended to clarify that 17.3% patients had prior exposure to adalimumab and a small number had prior exposure to other biologic therapies.

	biologic-experienced patients in the BE HEARD trials."		

Issue 22 Perspective on outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 65 in column 3 the text reads: *"Partly. QALY benefits for treated patients were considered through health state utility values.* *Health benefits on BSC based on assumptions which may not appropriately represent NHS outcomes."*	The text should read: "Yes. All direct health effects for patients, were considered."	The difference in the QALY benefit assumptions between treated and BSC patients should not have an impact on the perspective of outcomes in the economic model.	Agreed, this has been amended.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 69 the text reads: *"As the present model structure does not allow patients to regain response according to the transition probabilities based on the BE HEARD studies, it fails*	The text should be edited as follows: "As the present model structure does not include this 12-week stopping rule, it does not allow quantifying a potentially substantial additional	Patients in the model are allowed to lose or regain their response. UCB has accounted for secondary non-response through a discontinuation rate in	Not a factual error. An amendment has been made for clarity: "As the present model structure does not allow

to capture a potentially substantial component of the treatment effect associated with bimekizumab and secukinumab, and likewise fails to represent observed outcomes on maintenance treatment in the trials."	treatment effect associated with bimekizumab and secukinumab."	maintenance amongst week 16-responders.	patients to regain response whilst remaining on active treatment according to the transition probabilities based on the BE HEARD studies and NMA"

Issue 24 Unused tunnel states

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
On page 69 the text reads: *"However, the EAG note that the current company model is configured with a number of (unused) tunnel states that could be adapted to implement a simplified version of this stopping rule."*	The text should be deleted	The model has additional states to implement sequential treatments. It was not designed to handle the secukinumab modified stopping rule for secondary non-responders with tunnel states. Modifying the model to include the unique secukinumab stopping rule in secondary non-responders requires additional model adaptation.	Amendment made as suggested.

Issue 25 Transitions to higher levels of response for patients on BSC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 70 the text reads: *"As is discussed further in Section 4.2.6, transitions to higher levels of response were not possible for any patients on BSC between Week 16 and Week 48"*	The revision should read: As is discussed further in Section 4.2.6, transitions to higher levels of response were not possible, in the model base-case, for any patients on BSC between Week 16 and Week 48	The sentence is correct only for the base case analysis. The model allows the evaluation of several scenarios, that include transitions to higher levels of response.	Amended.

Issue 26 Benefits for patients discontinuing treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 70 the text reads: *"This awards the benefits of active treatment indefinitely to discontinuing patients, whilst incurring none of the costs associated with active treatment."*	The revision should read: This awards the benefits of active treatment indefinitely to patients discontinuing due to loss of efficacy. Patients who stop active treatment due to AEs before week 48 have lower response rates.	Before week 48 patients who stop active therapy for any reason have lower response rates.	Not a factual error. The preceding text adds the specific context in which this applies.

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 70 the text reads: *"Furthermore, patients who discontinue active treatment move into tunnel states applied in order to apply initial period transition probabilities for BSC."*	Please delete: "applied in order to".	This was an error on UCB's part that will be corrected in a future model. "In order to" implies that this error was by design. In clarification questions B1 and B2, the specific instances that the EAG had identified as problematic were not listed.	Agree that intent was implied. Text amended to the following: "move into tunnel states which apply initial period transition probabilities"

Issue 28 Availability of a working model with tunnel states for patients on BSC after week 48

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 70 the text reads: *"The EAG highlighted this issue at the clarification stage and requested that if the 'durable response' assumption were to be included in the model, that transition probabilities on BSC beyond Week 48 be applied only once a patient*	The text should be revised: However, the company stated this was not possible in the time available (2 days) given the complexity of the necessary structural changes.	The text does not explain that this was an additional question, sent after submission of clarification response with two days turnaround to implement the revisions.	Not a factual error. This question was clarified orally to the company at the clarification meeting. It was provided in written form by the EAG 15 days

who has discontinued bimekizumab or secukinumab has been on BSC for 48 weeks, rather than from Week 48 of the model time horizon (CQ B17.2). However, the company stated this was not possible in the time available given the complexity of the necessary structural changes."			prior to receipt of the company's response.

Issue 29 Sampling of patient baseline characteristics model parameters

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 71 the text reads: *"Whilst standard deviations are presented for patient characteristics, the probabilistic analysis presented by the company include no consideration of heterogeneity, and instead samples parameter permutations relating to patient characteristics from*	The text should be revised to explain that no probabilistic sampling was conducted on baseline characteristics	The PSA did not include the baseline characteristics, specifically for the reasons mentioned by the EAG. It is inaccurate to suggest that the model samples parameter permutations relating to patient characteristics.	Text amended to the following: "The probabilistic analysis presented by the company included no sampling of baseline characteristics".

the standard error of the mean from the BE HEARD I and II studies."			

Issue 30 TA935 and considerations on the generalisability of the trial population to the NHS.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 71 the text reads: *"A key issue raised by the committee in TA935 related to the generalisability of the trial population to the NHS with regards to prior biologic exposure"*	Remove the text.	From the TA935 final guidance: *The committee considered that there were some uncertainties about whether the SUNNY trials were generalisable to the decision problem. But on balance, it concluded that the results of the full trial population (that is, people who had and had not had biological treatments) were generalisable to the company's narrower target population. This was people with moderate to severe HS not able to have adalimumab, including people for whom adalimumab did not work or stopped working.*	Further clarity has been added as follows: "The committee in TA935 had concerns relating to the generalisability of the SUNNY trial populations to the NHS with regards to prior biologic exposure. However, on balance they concluded the full population was generalisable to that considered in the decision problem. The NHS population at this position is likely to predominantly comprise patients with previous

			exposure to adalimumab, but these patients make up only 18.8% of the trial population in the BE HEARD studies.

Issue 31 Secukinumab dosing frequency in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 72 the text reads: *"The company interpreted the maintenance dosing of secukinumab as 'monthly' rather than Q4W in the executable model."*	The text should be deleted.	UCB followed the secukinumab dosing label for patients with hidradenitis suppurativa, which states "monthly": *The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing.*	We have amended this for clarity to the following: "The company interpreted the 'monthly' maintenance dosing of secukinumab in the SmPC as every 4.3482 weeks, rather than as Q4W per TA935 in the executable model." This may reflect a lack of clarity in the licence documentation. The trials for secukinumab use a Q4W dosing frequency. This is reflected in the

			economic model in TA935, and the published NICE guidance. Dosing information provided to patients by the manufacturer of secukinumab states 'every 4 weeks'. Modelling secukinumab as Q4W is consistent with the approach accepted in TA935, and doing so results in reduced incremental costs for bimekizumab relative to secukinumab.

Issue 32

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 72 the text reads: *"The company provided a scenario analysis in their clarification response which implemented an*	Revise the text to clarify the scenario presented by UCB	UCB submitted no scenarios that included up-titration to secukinumab Q2W. UCB submitted a scenario (CQ B2) that reduced the proportion of	Not a factual error. The passage quoted does not state that UCB submitted a scenario inclusive of up-titration.

approximation of up-titration for secukinumab, but this was based on a 36-week extension of Q2W treatment to Week 48, rather than Week 28 as preferred by the company in TA935."		patients that would stop treatment due to non-response (<HiSCR25). This scenario clearly states that the reduction of the stopping rule only applied to week 48 (Table 34, p.56, company response to CQ).	The company's response to CQ B2 described a scenario which approximates the impact of a relaxed stopping rule on cost-effectiveness, where patients switch to Q2W dosing (at no additional cost), allowing patients to remain on treatment and potentially regain response. As the company considers the relaxed stopping rule for primary and secondary non-responders to apply only to secukinumab due to the inclusion of up-titration in the licence, the intent of this scenario is otherwise unclear.

Issue 33 Relaxed stopping rule for patients in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 72 the text reads: *"It was unclear whether the 'relaxed stopping rule' applied to primary non-responders, or to all patient"*	The text should be deleted	UCB explained in the clarification response that primary and secondary non-responders are not treated differently (see company response to CQ B2).	Thank you, this has been amended.

Issue 34 Citation for Garg et al. 2020

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 73 the text reads: *"This figure was based on an international survey of HS patients between October 2017 and July 2017"*	The text should cite the study it is referring to: Garg A, Neuren E, Cha D, Kirby JS, Ingram JR, Jemec GBE*, et al.* Evaluating patients' unmet needs in hidradenitis suppurativa: Results from the Global Survey Of Impact and Healthcare Needs (VOICE) Project. Journal of the American Academy of Dermatology. 2020;82(2):366-76.	No citation provided in the text.	Thank you, this reference has been added.

Issue 35 Use of adalimumab following loss of response to active treatment contradicts NICE guidance

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 73 the text reads: *"Given that the use of adalimumab following loss of response to secukinumab directly contradicts NICE Guidance (and is therefore not funded), the EAG considers this usage highly unlikely."*	The text should be revised to explain that this is the EAG's opinion and does not contradict NICE guidance.	The UCB model assumption does not directly contradict NICE guidance. When TA392 was produced, there were no licenced treatments for patients with HS. The guidance provides instructions on when to stop treatment. It provides no instructions on whether treatment can be re-initiated after other treatments have been tried. Treatments licensed in the UK may be used within their licence if appropriately prescribed, and this usage would not be inconsistent with adalimumab's licence or NICE guidance. As noted in the CS, clinical advice to UCB during pre-submission review of the CS was that the proportion of patients retrying	Amended to the following: "It is the EAG's understanding that the re-initiation use of adalimumab following loss of response to secukinumab is unlikely to be reimbursed on the NHS, and thus the EAG considers this usage highly unlikely." This issue can be clarified by NHS commissioning experts.

		adalimumab after failure of other treatments was an appropriate representation of NHS practice.	

Issue 36 Uncertainty about the efficacy of secukinumab up-titration dose

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 74 the text reads: *"If this approach to treatment leads to improved outcomes, the model may underestimate the efficacy of secukinumab."*	Add text to explain the uncertainty of this happening.	The evidence suggest uncertainty in the efficacy of Q4W and Q2W secukinumab dose. From the TA935 final guidance: *The committee noted that the SUNNY trials did not show a clear dose-response relationship for secukinumab (see section 3.5). So, it considered that there was substantial uncertainty in the application of up-titration in the company's model* *The EAG noted that the SUNNY trials were not*	Added the following text: "However, the effect of up-titration is uncertain, as dose-response relationships were unclear for secukinumab."

		designed to assess up-titration of treatment dosage.	

Issue 37 UCB scenario for reduced discontinuation due to loss of efficacy with secukinumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 74 the text reads: *"In their clarification response, the company present the results of a scenario which attempts to implement this approach based on an extension of Q2W treatment to Week 48 and the relaxation of the stopping rule for non-response."*	The text should be revised to explain exactly the scenario presented by UCB.	UCB did not present a scenario of secukinumab up-titration. Up-titration of secukinumab from monthly to Q2W administration has no additional cost compared to continuing treatment on a monthly dose. The efficacy data used to support the secukinumab submission provides no data showing that up-titration improves response. Given that the company in TA935 assumed identical efficacy for up-titration, including only the monthly dose will have no effect on efficacy or costs. As stated in CQ B2: The primary effect of such a tunnel state would be to	See response to Issue 32. We have amended the text to clarify that this is an approximation of the effect of up-titration.

		reduce discontinuation from secukinumab to BSC. In order to model this, UCB has conducted a scenario where the stopping rule for secukinumab is relaxed in line with transition probabilities from HiSCR<25 to any other state up to week 48. The results of the analysis (Table 34) showed minimal effect on the ICER. This scenario includes modifications made in response to B3.	

Issue 38 Discontinuation from bimekizumab and secukinumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 74 the text reads: *"Bimekizumab and secukinumab should only be discontinued when a patient stops responding during the maintenance phase and does not re-establish a response for 12 weeks."*	The text should be revised to reflect accurately the license of bimekizumab and secukinumab	The licence for secukinumab does not provide any hard rules for discontinuation. It does provide for up-titration where adequate clinical response is not attained or is lost. For this reason, UCB believe that the use of the modified stopping rule is consistent with the	Not a factual error. Secukinumab is funded for HS according to NICE Guidance. The conditions of reimbursement on the NHS may differ from the wording of the licence.

		secukinumab licence language on up-titration. The licence for bimekizumab does not contain language on up-titration. A maintenance dose of Q4W is the only licenced bimekizumab dose.	This stopping rule applied in this way comprises part of the committee's preferred assumptions in the FDG for TA935, and reflects the way in which stopping rules for secukinumab and bimekizumab should be modelled in the present appraisal. The EAG does not claim that up-titration should be modelled for bimekizumab or secukinumab.

Issue 39 Biologic-experienced patients model scenarios

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
On page 75 the text reads: *"Scenario analyses exploring the impact of using effectiveness data based on biologic*	The text should be deleted and the scenarios should be presented.	UCB provided transition matrices for the bio-experienced and bio-naïve treatment populations and described the adaptations	Not a factual error. A model inclusive of all requested functionality

experienced patients could not be presented in Section 6, as this model functionality or appropriate model inputs to perform subgroup analysis was not provided by the company upon request."		made to the base case model to produce analyses for these populations with the initial response to CQs. The transition matrices were presented to four decimal places. While UCB recognize that this can cause individual lines to not add up to 100%, this can be remedied by reweighting the lines. No biologic-experienced executable model was provided at this time. The EAG did not request UCB to run all scenarios using the bio-experienced population. Substantially after the initial response to clarification, the EAG requested executable models without rounded values. UCB provided bio-experienced and the bio-naïve model, as well as scenarios that were highlighted as important to the EAG.	should have been provided with the clarification response. This is for the purposes of validation and adaptation of the model. Simply providing rounded transition probabilities does not allow the EAG to replicate the model results and cannot be used to conduct probabilistic sensitivity analysis. As stated in the report, the uncertainty around the subgroup analysis results is a key issue. The EAG made this request one week after the company provided the post-clarification model. Models capable of replicating the company's subgroup analyses were only provided two days before

			submission of the EAG Report.

Issue 40 BSC transitions above the diagonal of the matrix set to zero

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 79 the text reads: *"Transitions to a higher level of response were simply set to zero (see Table 27)."*	The text should be revised: Transitions to a higher level of response were set to zero and the complement was adjusted (1-P).	The scenario did not simply set values above the diagonal of the matrix to zero. It adjusted the probabilities for the remaining states so that the transition probabilities were coherent.	Amended to the following: "Transitions to a higher level of response were simply set to zero (see Table 27), and the remaining probabilities were renormalised."

Issue 41 BSC effect underestimated

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 82 the text reads: *"approach also has the effect of increasingly*	Suggest adding additional wording to clarify that this is an opinion of the	The efficacy of BSC over time is not established in facts. It is impossible to say	Not a factual error.

underestimating the outcomes of patients on the BSC arm over time"	EAG rather than a fact, or removing statement.	whether UCB's estimates are over or under-estimates. It is sufficient to say that the EAG finds alternative assumptions more plausible. Statements of this type state as fact claims that the EAG does not have the knowledge to validate and cannot substantiate with data.	As discussed in the surrounding text and Table 29, the gradual deterioration assumption clearly results in substantial underestimates of observed response on BSC in PIONEER II. This section makes many comparisons with observed data in PIONEER II. The text has been amended to: "…has the effect of increasingly underestimating the observed outcomes of patients on the BSC arm over time".

Issue 42 Context on the assumptions of response in the BSC arm in TA935

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 84 the text reads: *"the EAG note that the committee considered a plateau in response rates for the BSC arm to lack face validity in TA935"*	Add text that it is the EAG analysis of TA935 that were deemed to be lacking face validity by the committee.	The revised description adds context. In TA935, the EAG estimated a placebo response in the long-term that plateaued at greater than 30%. The committee and clinicians considered this high level of response on BSC to lack face validity. The committee had no specific discussion and the guidance makes no specific comment about considering a lower level of plateau for BSC..	Not a factual error. The FDG states the following: "the committee considered that the plateau in the response rates for the BSC arm of both the company and the EAG base case lacked face validity." And that "The point at which the curve plateaued was substantially lower in the company's base case than in the EAG's base case." However, the text has been amended for clarity:

			“the EAG note that the committee considered a the alternative plateaus in response rates for the BSC arm presented by the EAG and company to lack face validity in TA935”

Issue 43 Timelines for request for additional analyses post clarification question response

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 86 states: *"This was explicitly not referring to up-titration as stated by the company in their clarification response."*	Please revise the text to acknowledge that the additional analyses to investigate secondary non-response within the model was requested after the submission of the response to clarification questions and that the timeline given was short (2 days).	The company would have been happy to conduct the requested analysis had it been feasible to investigate, implement within the model and subsequently validate the results in the timeframe given. In two days it was not feasible.	Not a factual error. In EAG clarification question 2b, the EAG requested and specified a correction of secondary non-response in alignment with that accepted in TA935. This request comprised part of the original clarification response, and the company did not address this issue. It is unclear to what the company are referring to here.

Issue 44 Use of language

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 86 states: *"Through failing to implement this stopping rule, the company's base-case analysis will (potentially significantly) underestimate treatment costs and the proportion of patients who regain and retain a response to bimekizumab and secukinumab."*	Please revise text as so: *"Through not implementing this stopping rule, the company's base-case analysis <u>may</u> (potentially significantly) underestimate treatment costs and the proportion of patients who regain and retain a response to bimekizumab and secukinumab."*	The language in the report is definitive and would be more appropriate to acknowledge that while the EAG believes other assumptions to be more appropriate it does not mean there are not ways to ascertain the direction or approximate magnitude of effect in the model.	Not a factual error. These are factual statements about the functionality of the executable model and are demonstrated in scenario analysis. Relaxing the stopping rule will by definition increase time on treatment and thus treatment costs. By applying BKZ/SEC transition probabilities to those who lose response, patients will be able to regain and retain response to treatment.

Page 86 states: *"The EAG considers the omission of the opportunity for patients to regain response rather than immediately discontinuing to substantially overestimate the rate of discontinuation on active therapy."*	Please revise text as so: *"The EAG considers the omission of the opportunity for patients to regain response rather than immediately discontinuing <u>may</u> substantially overestimate the rate of discontinuation on active therapy."*		Not a factual error. This is a demonstrable effect of relaxing the stopping rule for secondary non-responders in the model.
Page 87 states: *"This introduces very substantial uncertainty into the results and means total and relative QALY gain on each treatment option cannot be ascertained in the current model structure."*	Please revise text as so: "*This introduces very substantial uncertainty into the results and means total and relative QALY gain on each treatment option <u>may be underestimated</u> in the current model structure."*		Not a factual error.

Issue 45 Additional contextual information regarding Lee et al. 2022

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 88 states: *"The crude SMR applied to represent disease-related mortality (1.86) was obtained from*	Please provide additional information.	While the description of the study as a 'cohort' is technically accurate, context that the study a large-scale real-world epidemiology study	The text has been amended.

cohort study of patients with HS in Korea"		that included 56,228,437 patients of which 26,304 patients had HS may be useful insight.	

Issue 46 Clarification question B4c

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 88 states: *"The EAG requested that the company justify the use of the crude HR over this adjusted value (CQ B4.c), but no response was provided."*	Please revise the text. UCB did provide an explanation in CQ B4.	As stated in the company's response to CQ B4: "HS is a causal factor in comorbidities that contribute to increased mortality." As detailed in the description of the patient experience with moderate to severe HS in the company submission, HS contributes to many comorbidities that reduce health and increase mortality because of the underlying disease mechanisms. It follows that it would be inappropriate to adjust for these comorbidities because such adjustment would remove HS effects on	Not a factual error. No response was provided to this clarification question. The text referenced here refers to CQ B4.c. Whilst 'it may follow' that adjustment for comorbidities is inappropriate as stated here, B4.c requested justification with reference to the methods of adjustment used in Lee *et al.*

		mortality by assuming that HS patients would be expected to have similar rates of these comorbidities to the overall population.	

Issue 47 Clarification question B5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 90 reads: *"The EAG requested evidence specifically in support of the statistical significance of this difference across treatment phase (CQ B5), but no response was provided by the company."*	Please add text to acknowledge that the company conducted further scenario analyses in response to CQ B5 around the health state utility values, and that there was limited impact on the results.	This is a miscommunication as UCB interpreted the EAG's question around the significance of using treatment specific utilities to mean their impact on the results as opposed to referring to statistical significance. The company provided several scenarios on the health state utility values and impact these have on the cost-effectiveness of bimekizumab.	Not a factual error.

Issue 48 Utility values reported by treatment phase

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 91 states: *"Whilst utilities recorded during the maintenance treatment phase were consistently higher by response state than those recorded during the initial phase, the company provided no evidence that these differences achieved statistical significance (upon request)."*	Please revise the text.	The company submission provided sufficient information to evaluate the likelihood of statistical significance between the initial and maintenance phases. Please see CS Table 63, which provides mean utilities and standard errors for utility scores on active therapy in the initial treatment and maintenance phases. For CQ B5, the company focused on providing alternative scenarios to satisfy EAG requirements. In line with Bayesian principles, the appropriate yardstick is not statistical significance, but the balance of probabilities as is captured in the probabilistic sensitivity analysis.	Text revised to the following: "…there was no evidence that these differences achieved statistical significance."

Issue 49 Utility values on BSC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 92 states: *"The company's base-case analysis did not weight BSC initial period utilities for the inclusion of adalimumab. This appears to be inconsistent with the argument that patients treated with biologics will have improved HRQoL."*	Please revise the text.	There is no inconsistency. Patients randomised to placebo are likely to benefit from a placebo effect to their utilities before week 16. In the maintenance phase, patients know they are on adalimumab which would support having higher utilities. In the absence of data to suggest the magnitude of any placebo effect, we have included placebo effect in maintenance utilities for BSC patients in addition to including the benefits of active therapy.	Not a factual error.

Issue 50 Dosing of secukinumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In table 32 on page 93, and again on page 94 where it	Please revise the text where appropriate.	The company have modelled secukinumab in line with the	See response to Issue 31.

states: *"The EAG considers this to be an error in the company's interpretation of the licence for secukinumab and corrects this to one dose per model cycle for consistency with the accepted modelling approach in TA935."*		SmPC where it states: *"The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing."*	The company's interpretation of the licence appears to differ from that of the manufacturer of secukinumab and NICE. It is also inconsistent with the secukinumab pivotal trials. The EAG highlights that this correction benefits the company.

Issue 51 Resource use population weighting

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 95 states: *"In the submission, the company state that resource use frequency is 'adjusted to severity in BE HEARD I and II', but no further explanation was provided."*	Please revise the text: "In the submission, the company states that resource use frequency is 'adjusted to severity in BE HEARD I and II', the weightings were provided in response to the clarification questions."	The company provided the weights used in the calculations of the resource use to adjust for the severity in BE HEARD in the response to clarification question B12c.	Amendment made as suggested.

Issue 52 Confidential pricing arrangements

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In table 37 on page 98, the EAG present the confidential pricing arrangements for bimekizumab, secukinumab and adalimumab.	Please revise the table to include indication specific pricing arrangements.	Secukinumab has both a confidential simple PAS and an indication specific commercial PAS that allows free up-titration to Q2W in HS. Additionally, in TA392, adalimumab had an indication-specific simple PAS that was stated in NICE's final guidance.	Not a factual error. Table 37 presents the source of the confidential prices used in the confidential appendix. The non-confidential arrangements for secukinumab, and historic pricing agreements for Humira are not relevant to the confidential appendix.

Issue 53 Company submission scenario replication

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 103, the EAG provides their results for scenario 6 as outlined in the company submission.	Please update the analysis and subsequently revise the text.	The EAG has seemingly left one of the variable/controls to a previous setting or misinterpreted the controls for	The results for CS Scenario 6 have been removed from Table 42. Reference to this

		the loss of response for BSC w48+ and applied a 0.1 RR.	replicability issue has been removed. Thank you for highlighting this issue. For reference, the company's scenario switch for the 'loss of response' assumption automatically applies a 0.1 RR.

Issue 54 Proportion of patients modelled in maintenance

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 108 states: *"The model predicts that around [redacted] of patients entering the maintenance phase with at least a partial response will have discontinued by Week 48."*	Please revise the text.	The EAG appears to have made an error in the calculation. Subtracting week discontinuation after week 16 (represented by week 20), and discontinuation after week 48 (represented by week 52) results in [redacted]	This value refers to the half-cycle corrected patient distribution. At Week 20, [redacted] of those on bimekizumab remain on treatment in the model. At Week 52,

		[redacted]) of patients with partial response or better discontinuing between week 16 and 48.	[redacted] remain alive and on treatment. Therefore, [redacted] are modelled to have discontinued during this period. This was reported as an approximate figure, but the in-text figure has now been updated to report to one decimal place throughout the report.

Issue 55 BE HEARD discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 108 states: *"This compares to a value of [redacted]% over the equivalent period in the BE HEARD studies"*	Please revise the text.	The BE HEARD trials do not include a stopping rule, so the implied stopping rule would be higher than discontinuation between week 16 to 48. It is not clear how the EAG has calculated this value, but it is likely incorrect or based on an incorrect premise.	Not a factual error. The figure of [redacted] simply refers to the all-cause discontinuation rate in the BE HEARD studies used to calculate the risk of 'all-cause'

			discontinuation during the maintenance period in their original company model. On Page 137 of the CS, the company state that for patients in the Q2W/Q4W arms of the BE HEARD I and II studies: "From [redacted] patients starting maintenance after at least partial response, [redacted] discontinued from the study during the maintenance treatment period". That is, [redacted] of patients entering the maintenance period with a partial response had discontinued by the end of the maintenance period. [redacted] discontinued due to adverse events.

			The EAG report has been amended to reference these numbers of patients in the first instance this percentage is calculated.

Issue 56 Clarification of scenario 8 described by the EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 108 describes a scenario presented by the EAG to allows some patients to regain response and continue treatment.	Please clarify which patients this applies to i.e. maintenance.	It is not clear from the report that this stopping rule should only apply to patients that are in maintenance.	This scenario explicitly refers to secondary non-responders. The text has been amended for additional clarity.

Issue 57 Surgery costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 110 describes the weighting used by the EAG in further analyses and	The sentence should be revised to explain that the TA935 value is higher than that used in Scenario 16.	The cost in TA935 is different to that used by the EAG.	Not a factual error.

states that this is in line with TA935.			Section 6 of the EAG Report describes the assumptions and parameters used in each of the scenarios described. These descriptions refer back to relevant detailed critique. The EAG's critique on Page 96 sets out these figures and describes why this value is higher than that applied in TA935 due to the use of the latest NHS Reference Costs.

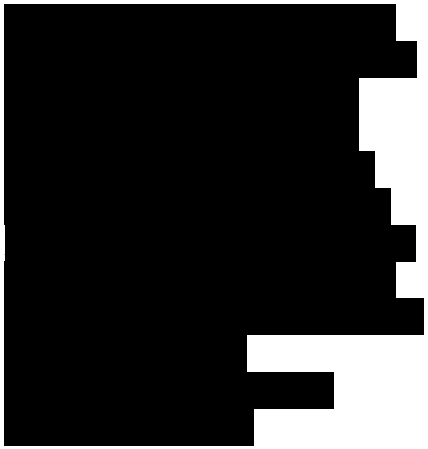
Issue 58 Model provision

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 122 states: *"However, a model was not provided in time for integration into the EAG Report. This remains a substantial area of uncertainty."*	"The company provided a model, and transition matrices for both biologic naïve and experienced patients as part of the response to clarification questions."	The company response to clarification questions provided transition probability matrices to allow modifying the base case model to run bio-experienced and bio-naïve populations (see CQ B16). Executable models that integrated these transition matrices were provided in response to an additional EAG request after the company clarification question response was submitted. The company's additional response also provided results tables for analyses that the EAG highlighted as important in communications to UCB via NICE.	See response to Issue 39. A model inclusive of all requested functionality should have been provided with the clarification response. This is for the purposes of validation and adaptation of the model. Simply providing rounded transition probabilities does not allow the EAG to replicate the model results and cannot be used to conduct probabilistic sensitivity analysis. As stated in the report, the uncertainty around the subgroup analysis results is a key issue.

Issue 59 Up titration scenario of secukinumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 122 details *"The EAG were also concerned that the company were unable to provide a scenario analysis inclusive of up-titration of secukinumab in alignment with previous appraisals and the product's marketing authorisation."*	We suggest the following edit: "In alignment with TA935, a scenario analysis investigating the up titration of secukinumab was not provided by the company."	Up titration was not modelled in the final TA935 model, as detailed in the final guidance ("*The committee concluded that it was not possible to robustly model the inclusion of up-titration in the model. So, it preferred to remove up-titration in the base case.*").	We have removed reference to the company in this statement, reframing it as an unresolved uncertainty: "There remains uncertainty regarding the cost- and clinical-effectiveness of up-titration of secukinumab, in alignment with the product's marketing authorisation."

(please cut and paste further tables as necessary)

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.	
Page 43 details data from the clinical study reports (CSRs)	“The clinical study reports (CSRs) referred to only two infection-related dose interruptions in BE HEARD I and two in BE HEARD II; they did not lead to study discontinuation and resolved. It is unclear if these were the only dose interruptions to have occurred, or whether dose interruptions had any effect on outcomes. In any event, it is unknown if any of these dose interruptions occurred in the biologic-experienced subgroup.”		Thank you – this has been amended.
NMA and MAIC results			
Page 81 Figure 9	Both plots (A and B) should be marked as confidential in Figure 9	All plots in Figure 9 should be marked confidential	Thank you, this has been amended.

Page 84 bimekizumab response rates	"This assumption results in response rates of around 26% in the bimekizumab arm in perpetuity, despite >99% of patients having discontinued active treatment."	"This assumption results in response rates of around [redacted] in the bimekizumab arm in perpetuity, despite >99% of patients having discontinued active treatment."	Thank you, marking has been updated in two places where this figure is cited.
Page 87 mentions the likelihood of patients on bimekizumab regaining response.	"In any given cycle during the maintenance treatment period and beyond, a non-responder on bimekizumab should have a probability of around 24% of regaining at least a partial response on the basis of the BE HEARD transition probabilities."	"In any given cycle during the maintenance treatment period and beyond, a non-responder on bimekizumab should have a probability of around [redacted]% of regaining at least a partial response on the basis of the BE HEARD transition probabilities."	Thank you, this has been amended.
Page 122 details the impact of a combination of assumptions which should be redacted as that information has not been included or was redacted in the company's submission.	"This combination of assumptions generates around 75% the incremental benefits of bimekizumab"	"This combination of assumptions generates around [redacted] the incremental benefits of bimekizumab"	The EAG does not consider this fact to be confidential as it is not reporting confidential-marked data from the submission or model.

(Please add further lines to the table as necessary)