NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Bimekizumab for treating moderate to severe hidradenitis suppurativa

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using bimekizumab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: September 2024

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using bimekizumab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 30 October 2024
- Second evaluation committee meeting: 13 November 2024
- Details of the evaluation committee are given in section 4

Issue date: September 2024

1 Recommendations

1.1 Bimekizumab is not recommended, within its marketing authorisation, for treating active moderate to severe hidradenitis suppurativa (acne inversa) that has not responded well enough to conventional systemic treatment in adults.

1.2 This recommendation is not intended to affect treatment with bimekizumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

Usual treatment for active moderate to severe hidradenitis suppurativa when conventional systemic treatment (such as oral antibiotics) has not worked well enough is adalimumab. If this is not suitable, does not work well enough or stops working, secukinumab is an option. For this evaluation, the company asked for bimekizumab to be considered in the same population as for secukinumab.

Clinical trial evidence shows that bimekizumab is more effective than placebo for treating the symptoms of moderate to severe hidradenitis suppurativa. But bimekizumab has not been directly compared in a clinical trial with secukinumab. The results from an indirect comparison are uncertain. So, it is unclear how well bimekizumab works compared with secukinumab.

Because of the lack of data and the way the model has been structured, the cost-effectiveness estimates are also uncertain. It is not possible to determine the cost effectiveness of bimekizumab without further analyses from the company. So, bimekizumab is not recommended.

2 Information about bimekizumab

Marketing authorisation indication

2.1 Bimekizumab (Bimzelx, UCB) is indicated for 'the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS [hidradenitis suppurativa] therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for bimekizumab.

Price

2.3 The list price of bimekizumab is £2,443 for 2 x 160mg/ml (1 ml) pre-filled syringes (excluding VAT; BNF online accessed August 2024). The company has a commercial arrangement. This makes bimekizumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by UCB, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Hidradenitis suppurativa (HS) is a painful, long-term skin condition that causes abscesses and scarring. The exact cause of HS is unknown but it occurs in skin folds where there are sweat glands, in particular the groin and armpits. It affects about 1 in 130 people in the UK and is more common in women than men. It is particularly common in people of

childbearing age, people with a higher body weight and people who smoke. Symptoms can range from mild to severe. Early symptoms include isolated, painful nodules with or without intermittent inflammation. Symptoms may progress to abscesses and pus-discharging tunnels, known as sinus tracts and fistulas. The clinical experts advised that the scarring associated with HS can limit function and reduce the ability to work and study. Reversal of scarring may need extensive surgery, which has a 3- to 6-month recovery period. The extent and severity of HS are often determined using the Hurley staging system. The focus of the company's submission is moderate (Hurley stage 2) to severe (Hurley stage 3) HS. The patient and clinical experts stated that HS has a substantial effect on people's quality of life. The clinical experts emphasised that pain is a key symptom of HS and very high pain scores are often reported by people with HS. The patient experts explained that they experience physical pain and discomfort as a result of HS, which affects their daily life. This was supported by responses from a survey (n=21) seeking the views of people with HS, which demonstrated its many impacts. The patient experts explained that HS has a substantial impact on mobility, mental health and personal care. They added that weight loss has been recommended to them to help their condition. But because of the pain they experience it is often not possible to exercise, which further exacerbates the condition. They also advised that many people with HS experience long delays in diagnosis. This was supported by the results of the HS survey, in which one-third of respondents said it took longer than 10 years to be diagnosed from the time of first having symptoms. The patient experts explained that people are often initially misdiagnosed, for example, with sexually transmitted infections, in-growing hairs or folliculitis. The committee concluded that moderate to severe HS can substantially affect health-related quality of life.

Clinical management

Current treatment pathway

3.2 Guidelines from the British Association of Dermatologists and the Primary Care Dermatology Society recommend starting treatment for HS with conventional systemic treatment. This includes offering oral tetracyclines for at least 12 weeks, followed by oral clindamycin and rifampicin when oral tetracyclines have not worked. The guidelines recommend that retinoids such as acitretin or the anti-inflammatory antibiotic, dapsone, may be considered when earlier treatments have not worked. The clinical experts explained that people often cycle through multiple courses of antibiotics, but these rarely control moderate to severe HS. They also explained that every person is different, and the types of treatments offered in clinical practice are tailored to the individual. NICE's technology appraisal guidance on adalimumab for treating moderate to severe hidradenitis suppurativa (TA392) recommends adalimumab for moderate to severe HS in adults whose condition has not responded to conventional systemic treatment. The clinical experts explained that almost all people with moderate to severe HS will be offered adalimumab. Adalimumab is contraindicated in some people, and some people prefer not to have it. Adalimumab may also work at first but then stop working, which is described as secondary failure or secondary non-response. The clinical experts explained that adalimumab may be supplemented with other conventional treatments if symptoms start to worsen. TA392 recommends that response to adalimumab should be assessed after 12 weeks. Treatment should only continue if there is clear evidence of response, defined as:

- a reduction of 25% or more in the total abscess and inflammatory nodule count and
- no increase in abscesses and draining fistulas.

NICE's technology appraisal guidance on secukinumab for treating moderate to severe hidradenitis suppurativa (TA935) recommends secukinumab 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, has not worked or has stopped working. So, secukinumab can be used by people whose condition does not respond to adalimumab, or people for whom adalimumab is unsuitable. TA935 recommends assessing response to secukinumab after 16 weeks. Treatment should only continue if there is clear evidence of response, defined as:

- a reduction of 25% or more in the total abscess and inflammatory nodule count and
- no increase in abscesses and draining fistulas.

In current clinical practice, people whose condition does not respond to secukinumab are offered best supportive care (BSC). BSC may include topical antibiotics, oral antibiotics, dapsone, retinoids, ciclosporin and anti-androgens. The patient and clinical experts noted limitations with current treatment options. They stated that many of the current treatment options cause severe adverse events leading to stopping treatment. They noted that some treatments may be contraindicated for certain people, further limiting the availability of effective treatments. The committee agreed that the treatment pathway presented by the company, based on the British Association of Dermatologists' guidelines, broadly reflects treatments used in NHS practice. But it noted that treatment is tailored to the individual. It concluded that there is an unmet need for further treatment options for moderate to severe HS.

Proposed positioning and comparators

3.3 The marketing authorisation for bimekizumab is for active moderate to severe HS in adults when the condition has not responded well enough to conventional systemic HS treatment. The company positioned bimekizumab for active moderate to severe HS in people who cannot have adalimumab, or when adalimumab has not worked or stopped working. This is a narrower population than covered by the marketing authorisation. The comparators in the company's submission are

secukinumab and BSC. The clinical experts advised that they considered the company's positioning of bimekizumab appropriate. This is because in NHS clinical practice, adalimumab is offered following inadequate response to conventional therapy because of the lower price of adalimumab biosimilars. The committee concluded that the company's positioning of bimekizumab in the treatment pathway was appropriate. But it noted that the clinical data for bimekizumab from the pivotal trials was predominantly for people with moderate to severe HS who had not previously had treatment with a biologic like adalimumab (see section 3.7).

Clinical effectiveness

BE HEARD trials

3.4 The company presented evidence from 2 identically designed, phase 3, randomised, double-blind, placebo-controlled trials: BE HEARD 1 (n=505) and BE HEARD 2 (n=509). These are collectively known as the BE HEARD trials. There were 4 arms:

- bimekizumab 320 mg every 2 weeks
- bimekizumab 320 mg every 4 weeks
- bimekizumab 320 mg every 2 weeks as initial treatment up to week 16, followed by bimekizumab 320 mg every 4 weeks as maintenance treatment
- placebo as initial treatment up to week 16, followed by bimekizumab 320 mg every 2 weeks as maintenance treatment.

The study duration was 48 weeks. But because people in the placebo arm of the trial were re-randomised to have bimekizumab every 2 weeks after week 16, comparative effectiveness data was not available after this timepoint. The primary outcome of the trials was the proportion of people with an HS clinical response score of 50 (HiSCR-50) at week 16. HiSCR-50 is defined as at least a 50% decrease in total inflammatory nodule count, with no increase in the number of abscesses or draining

tunnel count. Key secondary outcomes included HiSCR-75, flare status, changes from baseline in Dermatology Life Quality Index (DLQI) total score and worst HS skin pain, and HS skin pain response. In the company's pre-specified analysis, people who had any systemic antibiotic as HS rescue medication were classified as 'non-responders'. But the company decided that these analyses do not match expected clinical practice. So, the company's submission focused on an alternative post-hoc analysis in which people who had systemic antibiotics for reasons other than HS were not classified as 'non-responders' (p values were not presented). In this analysis, the proportion of people with HiSCR-50 was higher for bimekizumab 320 mg every 2 weeks (55.2% and 58.7%) compared with placebo (34.0% and 32.3%) across both trials at week 16. The company also presented results for a subgroup of people who previously had biological treatment, in line with its proposed positioning of bimekizumab. The results indicated that bimekizumab was superior to placebo, with a higher proportion of people who had bimekizumab every 2 weeks reaching HiSCR-50 at week 16 compared with placebo. The committee concluded that bimekizumab was clinically effective compared with placebo for people with moderate to severe HS.

Indirect treatment comparisons

3.5 Because there was no direct head-to-head evidence for bimekizumab compared with secukinumab, the company did a series of network-meta-analyses (NMAs). The NMAs used 16-week data from BE HEARD and from the secukinumab trials, SUNSHINE and SUNRISE (collectively known as SUNNY). Only the data from the 2 arms of BE HEARD in which people had bimekizumab 320 mg every 2 weeks until week 16 were used (n=580; see section 3.4) as this matched the recommended dosing in the marketing authorisation. It was not possible to do an NMA after 16 weeks because all people allocated to placebo in BE HEARD for bimekizumab, and in the SUNNY trials of secukinumab, transferred to active therapy after this timepoint. So, the company did a matching-adjusted indirect comparison (MAIC) of bimekizumab compared with secukinumab at

weeks 48 to 52. But only the NMAs were used to inform the economic model. NMAs were done for a range outcomes, including but not limited to HiSCR-50, HiSCR-75 and HiSCR-90 (results for these outcomes were used in the company's model). Based on a fixed-effects model at week 16, people having bimekizumab 320 mg every 2 weeks had a statistically significant higher odds of reaching all HiSCR response thresholds compared with secukinumab. Separate NMAs were also done for a subgroup of people who previously had biological treatment. For this subgroup, the results favoured bimekizumab 320 mg every 2 weeks for the HiSCR-50 and HiSCR-75 outcomes at week 16. But the results were not statistically significant. The committee questioned whether the clinical experts had noticed any differences in outcomes between bimekizumab and secukinumab in clinical practice. The clinical experts stated that there is not yet enough evidence from using bimekizumab in their clinical practice to reliably compare outcomes. But because of the difference in the mechanism of action of bimekizumab compared with secukinumab, it may be possible that it is more effective.

3.6 The EAG advised that patient characteristics were similar across the bimekizumab and secukinumab trials for most variables. But it noted that there appeared to be differences for potential outcome modifiers such as weight, body mass index, Hurley stage, DLQI, International Hidradenitis Suppurativa Severity Score System (IHS4) and antibiotic use. It noted that such inconsistency may affect the transitivity assumption in the NMA. But because there were no direct comparisons of secukinumab and bimekizumab in the network, it was not possible to formally evaluate inconsistency. For the MAIC, the EAG noted after adjustment of the selected 12 factors, all factors were identical in both trials to 2 decimal places. It found this highly implausible and suspected that either the data was incorrect or the matching was done incorrectly. The EAG advised that the results of indirect treatment comparisons (NMAs and MAIC) of bimekizumab with secukinumab should be treated with caution. The committee agreed with the EAG that differences between trials for

potential outcome modifiers added uncertainty to the results of the NMA, which in turn added uncertainty to the cost-effectiveness analysis. The committee also noted that the company did discrete NMAs for each of the HiSCR outcomes. It noted this approach can potentially result in lack of consistency between results for outcomes. It considered whether it may be more appropriate to do a single NMA using a multinomial likelihood model using a probit link to estimate HiSCR response. This NMA approach had been used for estimating Psoriasis Area and Severity Index response in NICE's technology appraisal guidance on bimekizumab for treating moderate to severe plaque psoriasis (TA723). It requested clarification from the company about whether this approach was considered in the current evaluation. It concluded that the comparative effectiveness of bimekizumab and secukinumab is uncertain. It also concluded that it may be appropriate for the company to consider doing an NMA using a multinomial likelihood model using a probit link to estimate HiSCR response.

Generalisability of BE HEARD results to the decision problem

3.7 The company positioned bimekizumab for active moderate to severe HS in people who cannot have adalimumab, or when adalimumab has not worked or stopped working (see section 3.3). The EAG noted that BE HEARD included people with moderate to severe HS, irrespective of whether they had previous adalimumab treatment. About 18.8% of people in BE HEARD previously had biological treatment, and 17.3% of people previously had adalimumab. The EAG was concerned that the overall population of BE HEARD did not match the company's positioning of bimekizumab. It advised that results based predominantly on a population that had not previously had a biological ('biological-naive') may overestimate the benefits in the target population. This is because people whose condition has previously not responded to biological treatment may be at increased risk for also not responding to subsequent biological treatment. The EAG noted that a small number of people who previously had biological treatment had treatments other than adalimumab. So, the

'biological-experienced' subgroup does not necessarily include all people whose condition does not respond to adalimumab and does not precisely match the company's target population. It also noted that restricting the analysis to only people who had previously had a biological substantially reduces the sample size of the population from BE HEARD (n=191). The sample size is reduced further when considering the population most relevant to the decision problem. That is, people who have previously had biological treatment having either the recommended dose of bimekizumab (n=115) or placebo (n=29). The company provided scenarios with a subgroup of people who previously had biological treatment, which demonstrated similar costs and quality-adjusted life years (QALYs) between the overall population and subgroup populations. The committee noted that the BE HEARD results to week 16 for the 'biological-experienced' and 'biological-naive' subgroups suggested minimal differences between outcomes for the subgroups. It also noted that the results for the 'biological-naive' subgroup are relevant for people who cannot take adalimumab. It heard from clinical experts that this group (people who cannot take adalimumab) is expected to represent about 5% of the target population. It agreed with the EAG that there may be uncertainty about whether previous lack of response to a biological might increase the risk of subsequent lack of response to a biological. It decided there were uncertainties about whether the BE HEARD populations were generalisable to the decision problem. But, on balance, it concluded that the results of the full trial population including the 'biological-experienced' and 'biological-naive' populations were generalisable to the company's target population and the decision problem.

Economic model

Company's modelling approach

3.8 The company developed a Markov model with 6 mutually exclusive health states based on 5 categories of HiSCR response, and an absorbing death state. Lower HiSCR categories indicate a lower level of response and are

assumed to be associated with a poorer quality of life and additional management costs. The model health states included:

- non-response (HiSCR score below 25)
- partial response (HiSCR score 25 to 49)
- response (HiSCR score 50 to 74)
- high response (HiSCR score 75 to 89)
- very high response (HiSCR score 90 and above)
- death.

People were assumed to enter the model in the non-response health state. They had the primary intervention for 4 model cycles (that is, the initial treatment phase). Treatment response was assessed at week 16 (model cycle 4). Having a partial response (HiSCR-25 or above) at this timepoint was necessary to continue having treatment with the primary intervention. People in the active treatment arms (bimekizumab and secukinumab) who did not have a partial response at week 16 were assumed to switch to treatment with BSC. 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, people could transition between HiSCR response states at any time in the model. For the BSC arm, people could transition between HiSCR response states during the initial treatment phase. During the maintenance phase, people in the BSC arm could only remain in their current health state or move to a lower response category. After week 48 of the modelled time horizon, the company assumed that people in the BSC arm maintain their 48-week response level indefinitely. The committee noted several limitations with the company's model structure (see sections 3.10, 3.11 and 3.13).

Adalimumab as a component of BSC

3.9 BSC primarily comprised topical antibiotics, oral antibiotics, dapsone, retinoids, ciclosporin and anti-androgens. The company also assumed that BSC includes adalimumab for 20.8% of people. This figure was

based on an international survey of people with HS between October 2017 and July 2018 (Global VOICE study). The company justified the inclusion of adalimumab as a component of BSC based on evidence in NHS practice suggesting that a proportion of people would continue on biological treatment even after losing HiSCR-25 response. In the model, people who stop bimekizumab or secukinumab are assumed to switch to BSC (see section 3.11). The company's model does not distinguish between BSC as a comparator and BSC as a subsequent treatment. So, it is assumed that after stopping bimekizumab or secukinumab, 20.8% of patients would re-start treatment with adalimumab. The EAG stated that, according to its understanding, third-line use of adalimumab is not recommended by NICE and is not funded by the NHS. It agreed it is plausible that some people may continue to have a biological following partial loss of response. But it considered that re-starting a non-indicated therapy (that is, adalimumab) is unlikely. So, the EAG preferred to assume that 20.8% of people would continue on their current treatment after losing HiSCR-25 response (that is, bimekizumab or secukinumab) rather than switching to adalimumab. It modelled this assumption in both its base cases ('EAG base case 1' and 'EAG base case 2'; see section 3.18). The clinical experts stated that in some cases continuation of a biological after losing HiSCR-25 response would be considered in NHS clinical practice. This includes the possibility of re-starting adalimumab at third line. However, this would involve an in-depth discussion with the patient and the consideration of a range of additional factors. These include the level of response obtained, the adverse events experienced and the possibility to add on any concomitant treatments. But the clinical experts noted that the risk and benefit would need to be weighed up carefully. In the case of considering whether to restart adalimumab at third line, the clinical experts said they would also consider how the person's condition responded when adalimumab was stopped. The committee noted that some people would continue to have a biological at third line, rather than switching to BSC. But it decided there was uncertainty about

the proportion of those continuing a biological at third line, who would continue to have secukinumab, bimekizumab or adalimumab. So, in the absence of robust estimates of these proportions, the committee concluded that it would prefer to assume all people who stop biological treatment at second line would switch to BSC without a biological. That is, it would prefer to assume that 0% of people would have a biological after stopping active treatment.

Up-titration of secukinumab

3.10 There is a complex patient access scheme (PAS) for secukinumab in HS. This means that the dose given every 2 weeks is supplied to the NHS at a cost equivalent to the dose given every 4 weeks. The marketing authorisation for secukinumab allows for the standard 4-weekly maintenance dose to be increased to 2-weekly depending on response to treatment. This up-titration of secukinumab was modelled as a scenario in TA935. Specifically, at week 16, people who did not have a HiSCR-25 response had their dose up-titrated for 12 weeks, and only stopped treatment if they continued to have no response at week 28. For this evaluation of bimekizumab, the company did not include up-titration of secukinumab from 4-weekly to 2-weekly in its base case. It stated that SUNNY did not show a clear dose–response relationship for secukinumab. It also noted that in TA935 the committee preferred not to include the up-titration of secukinumab because it concluded that it was not possible to robustly model it. The EAG advised that the net effect on cost effectiveness of modelling the up-titration of secukinumab was uncertain. This is because modelling this would increase the total QALYs compared with bimekizumab because of a larger proportion of people having a response. But the total costs for secukinumab would also be higher because people would continue having treatment for longer. The EAG advised it would be useful for the company to include the up-titration of secukinumab as a scenario, in line with its marketing authorisation. The committee noted that in TA935 the committee decided that a potential

approach for applying up-titration of secukinumab in clinical practice may be:

- at week 16 (end of the induction phase), stop secukinumab if the HS has not responded to it (HiSCR score below 25)
- at week 16 (end of the induction phase), up-titrate secukinumab from the every-4-weeks dose to the every-2-weeks dose for HS that has partially responded to it (HiSCR score 25 to 50)
- after week 16 (maintenance phase), up-titrate secukinumab from the every-4-weeks dose to the every-2-weeks dose for HS that initially responded to it at week 16 (HiSCR score above 25) then stopped responding for a consecutive period of 12 weeks (HiSCR score below 25). Stop secukinumab if the HS has not responded after 12 weeks of the up-titrated dose.

A clinical expert agreed this would be a reasonable approach for the up-titration of secukinumab and that some people may benefit from up-titration in clinical practice. The committee noted that the decision to up-titrate secukinumab and the regimen for up-titration may vary person to person. It noted there is uncertainty about the impact of modelling secukinumab up-titration on cost effectiveness. It concluded that it would be useful to see a scenario in line with the potential approach for applying up-titration of secukinumab in clinical practice, as set out above and in TA935. It noted that this should be done using a series of tunnel states in the model.

Stopping rule for secondary non-responders

3.11 The company implemented a stopping rule in which people who lost response (HiSCR score below 25) to bimekizumab or secukinumab during the maintenance phase (that is, secondary ‘non-responders’) stopped treatment immediately. This is separate from the stopping rule for people with HS that did not respond to treatment at week 16 (that is, primary non-responders). The company stated that its stopping rule is consistent with

the licence for secukinumab, which does not provide any 'hard rules' for stopping treatment. The EAG noted that the stopping rule for secondary non-responders is inconsistent with the stopping rule accepted by the committee in TA935. That is, during the maintenance phase, secukinumab would only be stopped when HS has stopped responding for a consecutive period of 12 weeks. The EAG stated that the model does not capture the ability to regain and maintain a treatment response, and the costs associated with continuation of treatment. It noted that based on the BE HEARD results, a lower proportion of people whose condition responded to treatment at week 16 stopped treatment by week 48 compared with the proportion of people predicted to stop in the model in this same period. So, it advised that the model was unable to determine the relative effectiveness of alternative treatment options. It stated that it would prefer a stopping rule for secondary non-responders in line with that accepted in TA935. But it implemented an approximation of this stopping rule in 'EAG base case 2', assuming a smaller proportion of people (20%) in the non-response health state stop in a given cycle. It also implemented a scenario applying 12 weeks of active treatment costs to secondary non-responders after stopping treatment in 'EAG base case 1'. The clinical experts stated that, in clinical practice, treatment would not immediately stop after loss of HiSCR-25 response. A clinical expert added that an intercurrent event may temporarily cause a loss of HiSCR-25 response, so it would be unreasonable to stop treatment immediately. Concomitant treatments may also be added in an attempt to reestablish response. The committee decided it was reasonable to assume that active treatment would only be stopped in the maintenance phase when HS has stopped responding for a consecutive period of 12 weeks (in line with TA935). The committee questioned whether the EAG's scenario in which a reduced proportion of people in the non-response health state were modelled to stop treatment could serve as a suitable proxy to model the impact of this stopping rule. But the EAG stated that its scenario biases against treatments that have a higher rate of regaining response. This is because

the current model structure does not allow for the scenario to be implemented in a way that ensures people in the non-response health state who have not stopped treatment, do regain a response. So, the scenario assumes people in the non-response state, who have not stopped treatment, still incur treatment costs. The committee noted that the impact of its preferred stopping rule on cost effectiveness was uncertain. It decided that the most accurate way to model the stopping rule for secondary non-responders would be to use a series of tunnel states to track when people entered the non-response health state. The committee concluded that it would prefer to assume that secukinumab and bimekizumab are stopped when HS stops responding to treatment in the maintenance phase if non-response is maintained for 12 weeks. It noted that this analysis should be done using a series of tunnel states in the model.

BSC maintenance phase transition probabilities

3.12 Data beyond 16 weeks for placebo was not available from BE HEARD (see section 3.4). So, the company adjusted the BSC transition probabilities used for the initial treatment phase (weeks 0 to 16) to incorporate a gradual deterioration assumption for model weeks 16 to 48. That is, it assumed that people having BSC could only continue in their current health state or transition to a worse health state. The company used this approach based on feedback from 2 UK advisory boards, in which clinicians stated that people having BSC would not maintain response in the long term. The EAG stated that it had received clinical advice describing HS as characterised by periods of transient exacerbation and improvement. So, the EAG was concerned that the company's assumption of gradual deterioration did not appropriately capture the natural history of HS and would overestimate the proportion of non-response to BSC. It also noted that the proportion of people with at least a HiSCR-50 response at week 36 was lower in the company's base-case model compared with that in the placebo arm of the PIONEER 2 study (for adalimumab) at week 36. It was also lower than the proportion

at week 36 predicted using the company's NMA to derive transition probabilities for BSC after week 16. The EAG preferred to use the company's week-16 NMA to derive transition probabilities for BSC after week 16 in both its base cases. This allowed the possibility of regaining response to treatment after week 16 for those having BSC. The clinical experts stated that HS causes scarring, which gradually gets worse for people having BSC. So, despite the possibility of transient improvement, there would be a general worsening of symptoms over time. The committee noted there was substantial uncertainty about the long-term benefits of bimekizumab compared with BSC because of the lack of comparative data from BE HEARD after week 16. It noted that using the company's week-16 NMA to derive transition probabilities for BSC after week 16 may overestimate the proportion of people transitioning to better HiSCR response states. But it also noted that the company's base case approach resulted in a lower proportion of people with at least a HiSCR-50 response at week 36 compared with that in the placebo arm of PIONEER 2. The committee noted that the company provided a scenario modelling week 16 to week 48 transition probabilities for BSC assuming a long-term loss of response based on linear fit to PIONEER 2. It noted this was different from how the PIONEER 2 data was used in TA935 to model BSC transition probabilities. Specifically, in TA935, transition probabilities from the placebo arm of PIONEER 2 were preferred for modelling BSC transition probabilities from week 16. The committee requested clarification from the company about whether it had considered the approach used in TA935. The committee concluded that it would like to see a scenario using transition probabilities from the placebo arm of PIONEER 2 (as used in TA935) to model BSC transition probabilities for week 16 to week 48.

BSC durable-response assumption

3.13 The company assumed that people having BSC remain in their current health state indefinitely beyond model week 48. It stated that a plateau of treatment response for BSC was also modelled in TA392. The EAG noted

this assumption allows people stopping active treatment to potentially retain the level of response achieved indefinitely upon reaching week 48 in the model. This assumption has a large impact on cost effectiveness, particularly when combined with the application of placebo-response outcomes to people who stop active treatment (see section 3.14). The EAG noted that in the company's base case model, the value case for bimekizumab is built around the incentive to stop active treatment closest to week 48. It stated it would prefer a model structure that allows people having BSC to transition freely between health states indefinitely. This is so the treatment effect of bimekizumab is less dependent upon BSC assumptions. The EAG noted that, in principle, it is not opposed to a response-rate plateau. But this should be modelled such that the response-rate plateau is applied only when a person who has stopped active treatment has been on BSC for 48 weeks (rather than from week 48 of the model time horizon). Because major model structural changes would be required, including implementation of additional tunnel states, the company stated that it was not possible to implement this update to the model within the given timeframe. But it explained that work has started on implementing this update to the model. The committee noted that the company's implementation of the durable-response assumption for BSC adds substantial uncertainty to the cost-effectiveness analysis. This is because it allows people stopping active treatment to potentially retain the level of response achieved indefinitely. The committee noted that the durable-response assumption after 48 weeks interacts with the choice BSC transition probabilities from week 16 to week 48. So, it considered it necessary to see a scenario in which the durable-response assumption is applied only after a person who has stopped active treatment has had BSC for 48 weeks.

Transition probabilities after stopping active treatment

3.14 The company assumed that people who stopped bimekizumab or secukinumab switched to BSC and then had the initial treatment phase placebo-response outcomes from BE HEARD for 12 weeks. So, losing

response to active treatment resulted in a boost to response rates based on the placebo-response rate in BE HEARD. That is, people in the non-response health state can move to a response health state when active treatment stops. The EAG noted that when combined with the durable-response assumption (see section 3.13), this generated a significant proportion of the QALY benefit of active treatment in the company's base case. The EAG advised that a significant component of placebo response in a trial setting is a person's belief that they may be having an effective therapy, as well as regression to the mean. But in the NHS, a person unblinded to the fact they have stopped having active treatment may be unlikely to experience the benefit of placebo response (beyond the cycles of exacerbation and improvement inherent to HS and its management). The EAG preferred to apply maintenance-phase BSC outcomes to people from the point of stopping (rather than initial treatment phase BSC outcomes) and incorporated this in 'EAG base case 2'. The committee agreed with the EAG that in clinical practice, a person unblinded to the fact they have stopped having active treatment may be unlikely to experience the benefit of placebo response. It also noted the clinical experts' advice that there would be a general worsening of symptoms over time for people having BSC (see section 3.12). So, the committee decided that applying initial treatment phase outcomes to people who have stopped active treatment may overestimate the benefit of the subsequent BSC treatment. The committee concluded that it would prefer to apply maintenance-phase BSC outcomes to people from the point of stopping treatment.

Mortality

3.15 The company identified a retrospective population-based cohort study from Korea (Lee et al. 2022) that presented all-cause and cause-specific mortality risks for people with HS. The study reported a standardised mortality ratio (SMR) of 1.86 for people who had surgical procedures and noted that people who had surgery were more likely to have more severe HS. This study also reported an adjusted SMR of 1.48 that accounted for

current smoking status, drinking status, body mass index, Charlson comorbidity index and the presence of psychiatric diseases at the index date. The company considered that severity of HS is a causal factor in comorbidities that contribute to increased mortality risk in HS. So, people in the non-response health state would have an increased mortality risk. It used the SMR of 1.86 to calculate the increased mortality risk for people in the non-response health state in its base case. People in all other health states were assumed to have the same mortality risk as the general population. The company noted that this approach was used because it did not identify any evidence to inform the distribution of mortality risk based on HiSCR response levels. But it acknowledged that its base-case assumption may underestimate the mortality risk for people in the most severe health states. The EAG noted that excess mortality related to HS is also attributable to long-standing metabolic and cardiovascular comorbidities. It added that these are not fully resolved immediately upon having a response to treatment. So, it advised that it was uncertain whether people in the 'response' health states would be exempt from the excess mortality risk. In the EAG's base cases, it applied an SMR of 1.86 and an adjusted SMR of 1.48 to all health states, respectively. The clinical experts explained that HS is an inflammatory condition that can lead to issues such as cardiovascular problems, which increase the risk of mortality for all people with HS. They noted that effective treatment is expected to reduce this risk, but generally, it is expected that all people with moderate to severe HS may have an increased mortality risk. The committee concluded that it would prefer to apply an SMR of 1.48 to all health states in the model to reflect the increased mortality risk for all people with moderate to severe HS.

Analysis and implementation of utility values

3.16 BE HEARD collected EQ-5D-3L data throughout the trial periods. Using this data, the company used treatment arm- and treatment period- specific utility values for each of the health states. The exact utility values are considered confidential and cannot be reported here. The company stated

that treatment-specific utility values were accepted in TA935, in which trial data demonstrated a statistically significant health-related quality of life benefit for secukinumab compared with placebo for most HiSCR categories. It noted that, based on a repeated measures ANCOVA model using the BE HEARD data, a significant health-related quality of life benefit was observed for bimekizumab compared with placebo in the non-response and high response health states. So, it considered that treatment-specific utility values were suitable for this appraisal. The EAG considered that this did not justify the inclusion of treatment-specific utility values, noting that a significant health-related quality of life benefit was not observed for all response categories. It noted that in the company's base case, BSC initial treatment phase utility values were logically inconsistent with the high-response utility value lower than that of the partial response and response. It also advised there was no evidence to suggest that the differences in health-related quality of life between the initial treatment phase and maintenance phase by response state were statistically significant. But the company provided a scenario analysis with non-phase specific utility values that showed a minimal impact on cost-effectiveness results compared with phase-specific utility values. The company stated that the inconsistent BSC initial treatment phase utility values were because of low observation numbers for the high-response health state. The EAG preferred the use of an alternative set of utility values that used a treatment-specific utility only for the non-response health state in both its base cases. This is because it is clinically plausible for some people in the active treatment arm in the non-response state to have some level of HiSCR response below HiSCR-25. The committee decided that the appropriateness of treatment-specific utilities was uncertain. But, it noted that the choice of approach had a small impact on the cost-effectiveness results. It stated that further information about the statistical fit of the repeated measures ANCOVA model would be useful to determine whether treatment-specific utilities are appropriate. It requested clarification on whether the repeated measures ANCOVA model using an

interaction term between treatment and response state fitted the data better than the model without the interaction term.

Cost-effectiveness estimates

Company's and EAG's cost-effectiveness estimates

3.17 Because of the confidential commercial arrangements for bimekizumab, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. The fully incremental deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) for bimekizumab in the company's base case are higher than the range normally considered an acceptable use of NHS resources.

3.18 The EAG presented 2 base cases. It stated that 'EAG base case 1' removes model assumptions that it considers as either clinically implausible, or that artificially and selectively impose certain treatment benefits for bimekizumab. 'EAG base case 2' is based on a clinically plausible alternative set of assumptions, which it considered to more fairly represent differential cost-effectiveness of secukinumab and bimekizumab. The EAG considered 'EAG base case 2' was the most clinically plausible of the analyses presented. The fully incremental deterministic and probabilistic ICERs for bimekizumab in both the EAG's base cases are considerably in excess of the range normally considered an acceptable use of NHS resources.

Uncertainties in evidence and modelling assumptions

3.19 NICE's manual on health technology evaluations notes that the committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty about:

- the comparative effectiveness of bimekizumab and secukinumab (see section 3.6)
- the reduced sample size from BE HEARD having the licensed bimekizumab dose (see section 3.7)
- the proportion of people continuing to have a biological at third line who would have secukinumab, bimekizumab or adalimumab (see section 3.9)
- the impact of modelling secukinumab up-titration on cost effectiveness (see section 3.10)
- the impact of applying its preferred stopping rule for secondary non-responders on cost effectiveness (see section 3.11)
- the long-term benefits of bimekizumab compared with BSC because of the lack of comparative data from BE HEARD after week 16 (see section 3.12)
- the company's implementation of the durable-response assumption for BSC (see section 3.13)
- the appropriateness of treatment-specific utilities (see section 3.16).

The committee's preferences

3.20 The committee preferred the model to:

- assume all people who stop biological treatment at second line would switch to BSC without a biological (see section 3.9)
- assume that secukinumab and bimekizumab are stopped when the condition stops responding to treatment in the maintenance phase if non-response is maintained for 12 weeks (see section 3.11)
- apply maintenance phase BSC outcomes to people from the point of stopping treatment (see section 3.14)
- apply an SMR of 1.48 to all health states in the model to reflect the increased mortality risk for all people with moderate to severe HS (see section 3.15).

The committee's requests for additional analyses

3.21 The committee could not determine the most plausible ICER because of the high levels of uncertainty in the modelling assumptions. The uncertainty was mostly because of the company's implementation of the durable-response assumption and its interaction with other modelling assumptions. The committee would like to see the following additional exploratory or confirmatory work:

- clarification on whether the company had considered doing a single NMA using a multinomial likelihood model using a probit link to estimate HiSCR response (see section 3.6)
- consideration of doing a single NMA using a multinomial likelihood model using a probit link to estimate HiSCR response (see section 3.6)
- a scenario in line with the potential approach for applying up-titration of secukinumab in clinical practice as described in TA935 (see section 3.10)
- building tunnel states into the model to implement the analyses described in sections 3.10, 3.11 and 3.13
- clarification on whether the company had considered using transition probabilities from the placebo arm of PIONEER 2 to model BSC transition probabilities for week 16 to week 48 (see section 3.12)
- a scenario using transition probabilities from the placebo arm of PIONEER 2 (as used in TA935) to model BSC transition probabilities for week 16 to week 48 (see section 3.12)
- a scenario in which the durable-response assumption is applied only when a person who has stopped active treatment has had BSC for 48 weeks (see section 3.13)
- clarification on whether the repeated measures ANCOVA model using an interaction term between treatment and response state fitted the data better than the model without the interaction term (see section 3.16).

Other factors

Equality

3.22 The committee noted that the prevalence of HS is higher in women, particularly those of childbearing age, and in people from an African-Caribbean family background. The committee noted these are protected characteristics under the Equality Act 2010. But because its recommendation does not restrict access to treatment for some people over others, the committee agreed that this was not a potential equality issue.

Uncaptured benefits

3.23 The committee noted the company's statement that there may be further benefits not captured in the cost-effectiveness analysis:

- the use of HiSCR may not capture all quality-of-life gains. This is because HiSCR response does not comprehensively consider the impact of inflamed sinus tracts or fistulas, which is an important factor for quality of life. Also, the way HiSCR response is measured (see section 3.4) may miss nuances of a continuous treatment effect
- the positive effect of systemic treatment (that is, bimekizumab) on the success rate of surgery and ability to have surgery
- potential further benefits of treatment when used in a real-world setting because concomitant treatment with antibiotics is not restricted by trial protocol
- potential treatment benefits for people with comorbidities including axial spondyloarthritis and psoriatic arthritis, or with an elevated risk of psoriasis
- potential benefits for family members of people with HS.

The committee concluded that these potentially uncaptured benefits did not have a material effect on decision-making at the first committee meeting. This is because they were unlikely to outweigh the committee's

concerns about cost-effectiveness estimates and the amount of uncertainty about the most plausible ICER.

Conclusion

3.24 The committee agreed that further information is needed to decide all of its preferred modelling assumptions and to understand the full impact of the uncertainties. It concluded that it was not possible to recommend bimekizumab for treating moderate to severe hidradenitis suppurativa.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Baljit Singh

Vice chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

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Technical lead

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ISBN: [to be added at publication]

Issue date: September 2024