CONFIDENTIAL REPORT

Bimekizumab for treating moderate to severe chronic plaque psoriasis

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Lorna Hazell, Senior Research Assistant, Evidence Synthesis
Joanne Lord, Professor, Health Economics
Neelam Kalita, Senior Research Fellow, Health Economics
David Scott, Principal Research Fellow, Statistics.
Jonathan Shepherd, Principal Research Fellow, Evidence Synthesis.

Correspondence to Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
Wessex Institute
Alpha House
Enterprise Road, University of Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

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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 HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Lorna Hazell critically appraised the bimekizumab clinical effectiveness evidence and drafted the report. Joanne Lord critically appraised the cost comparison analysis, and drafted the report. Neelam Kalita critically appraised the cost comparison analysis, and drafted the report. David Scott critically appraised the network meta-analysis and drafted the report. Jonathan Shepherd critically appraised the bimekizumab clinical effectiveness evidence, the network meta-analysis and drafted the report. He is the project co-ordinator and guarantor.

Please note that: *Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are AIC have been bordered with yellow.*

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1 Summary of the ERG's view of the company's FTA case

1.1 The technology is pharmacologically similar to the comparator

Bimekizumab is a humanised immunoglobulin monoclonal antibody that binds to both IL-17A and IL-17F cytokines to inhibit the IL-17 pathway. The company submission (CS) states that, if recommended, bimekizumab would be the only available plaque psoriasis treatment with this dual selective inhibition of IL-17A and IL-17F.

Two of the chosen cost comparators also target the IL-17 pathway: ixekizumab (IL-17A inhibitor) and brodalumab (IL-17A receptor inhibitor). Expert clinical opinion to the ERG is that bimekizumab might offer an advantage over standard IL-17 inhibitors due to the additional IL-17F inhibition. The third cost comparator is an IL-23 inhibitor (risankizumab).

The ERG's interpretation (confirmed by our clinical expert) is that, as a biologic drug, bimekizumab is similar, overall, to the chosen cost comparators. Pharmacologically it may have more similarity to the IL-17 agents than to the newer IL-23 agents. Amongst the IL-17 agents bimekizumab appears to be distinctive due to its dual selective inhibition of IL-17A and IL-17F. The company suggests that this potentially translates into greater clinical efficacy for bimekizumab compared to other biologics. The ERG's clinical expert agrees this is plausible, though it cannot be known for certain at present.

1.2 The selected comparator is appropriate

The ERG considers that the company's chosen cost-comparators (risankizumab, ixekizumab and brodalumab) adequately represent the NICE recommended treatments for plaque psoriasis as a whole. In the company's network meta-analyses these were the three highest ranking treatments on the PASI 75 efficacy measure (75% reduction in Psoriasis Area Severity Index) after bimekizumab. Their credible intervals overlapped indicating similarity in effects.

Risankizumab was recommended by NICE on the basis of cost-comparison to the biologic drug Guselkumab (TA596). Guselkumab itself was also recommended by NICE based on a cost-comparison to the biologic drugs ixekizumab and secukinumab (TA521). Ixekizumab (TA442) and brodalumab (TA511) were recommended by NICE based on cost-utility analyses in

comparison to multiple biologic drugs available at the time of those appraisals. Thus, the chosen comparators can be regarded to be representative of existing NICE recommended treatments.

Expert clinical advice to the ERG suggests that these three comparator drugs would be expected to have a reasonable market share in the treatment of plaque psoriasis.

The company states that the assumptions and methods informing the current cost comparison analysis maintain precedent with the two previous cost comparison NICE FTAs in this indication (TA596 Risankizumab, TA521 Guselkumab). Throughout this report we therefore note instances of concordance/discordance with previous NICE appraisals in this indication, specifically appraisals of the three cost-comparators (i.e. TA596, TA442 and TA511), and the remaining cost comparison FTA (i.e. Guselkumab TA521).

2 Critique of the decision problem in the company's submission

2.1 Population

The NICE scope specifies the relevant population as adults with moderate to severe plaque psoriasis. The marketing authorisation for bimekizumab is expected to be for [redacted]

The company's decision problem is more specific: adult patients with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.

The decision problem is thus narrower than the scope and the marketing authorisation in terms of patient population. The company justifies this by stating their expectation that bimekizumab would be used as an alternative to other biologic therapies, specifically in adults with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. Furthermore, they state that the population aligns with the majority of previous appraisals for biologics in plaque psoriasis, including the most recently NICE recommended biologic, risankizumab (NICE TA596). The ERG considers this an acceptable justification for the purposes of this cost-comparison.

For patients on biologic treatment, the NICE psoriasis pathway states that switching to an alternative biologic should be considered if there is no response to a first biologic (primary

failure), or response to a first biologic is subsequently lost (secondary failure), or intolerance or contraindication. Expert clinical advice to the ERG suggests that some patients may switch biologic treatments multiple times during the course of their disease. However, there is no recommendation regarding which biologic should be used first. Therefore, the ERG assumes that patients eligible for bimekizumab, therefore, may be either biologic naive or biologic experienced. This is of significance for judging the generalisability of the bimekizumab clinical trials (see section 3.1.4.1 of this report), and the assessment of heterogeneity in the indirect treatment comparison (section 3.3.4).

2.1.1 Psoriasis severity

The ERG notes that whilst the company's decision problem specifies inclusion of patients with moderate to severe plaque psoriasis, NICE guidance on previously appraised biologics stipulates they should be used in patients with severe disease (i.e. not in patients with moderate disease). The ERG asked the company to clarify this discrepancy (clarification question A2). In their response the company point out that previous scopes of NICE appraisals of biologics have included moderate to severe plaque psoriasis patients, despite final appraisal determinations (FADs) specifying their use in severe or very severe disease. To align with these previous appraisals the company's decision problem population includes moderate to severe psoriasis, but with the caveat that they expect a NICE recommendation for bimekizumab would similarly restrict its use to patients with severe disease (thus following NICE precedent).

The company's definition of severe psoriasis is identical to the definition of severe disease used in existing NICE guidance (i.e. based on PASI and DLQI score, and prior use of, or contraindication to, other systemic treatments and phototherapy). The ERG's clinical expert agrees that this indicates severe psoriasis.

The restriction of the decision problem to a narrower patient population has implications for the choice of comparator treatments in the scope, as discussed next.

2.2 Comparator

The NICE scope lists two sets of criteria with regard to relevant comparator treatments:

- Those for whom systemic non-biological treatment or phototherapy is suitable
- Those for whom conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated

Given the restricted decision problem population, only the treatments available for 'adult patients with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated' are eligible comparators for bimekizumab. The company has selected three NICE recommended biologics for cost comparison to bimekizumab:

- Risankizumab (NICE TA596)
- Ixekizumab (NICE TA442)
- Brodalumab (NICE TA511)

In an FTA, eligible comparators have to have been recommended by NICE for the same indication as the current appraisal. Only one of the scoped comparators needs to be selected. In this instance all three of the company's chosen comparators meet this requirement.

2.3 Outcome

The outcomes specified in the company's decision problem are broadly aligned with those in the final NICE scope. The company did not have sufficient data to explore the impact of treatment on psoriasis of the face or genitals (included in the scope). This limitation was also noted in the NICE appraisals of the three cost comparators (TA596, TA442 and TA511).

The ERG notes that a PASI 90 or PASI 100 response (90% or 100% reduction in PASI score from baseline) is considered an important therapeutic goal, aiming to achieve complete or near complete clearance of psoriasis. However, the less stringent PASI 75 response (at least a 75% reduction in PASI score) has been considered an adequate measure to ensure continuation of therapy in previous NICE appraisals, and for this reason the company have selected it as the key input for the cost comparison in the current CS. The ERG's clinical expert considers PASI 75 to be a clinically meaningful indicator of response to induction therapy used in practice, and patients achieving this would then be considered eligible for maintenance therapy. Clinicians would aim for PASI90 or PASI100 response for patients on long-term treatment.

3 Summary of the ERG's critique of clinical effectiveness evidence submitted

3.1 Clinical evidence submitted by the company

3.1.1 The company submission

The CS comprises a main evidence submission (Document B), a summary (Document A) and appendices to Document B. The company also provided relevant clinical study reports for bimekizumab and additional information in response to clarification questions from the ERG. Four multi-centre phase III/IIIb double-blind randomised controlled trials, BE-READY, BE-VIVID, BE- SURE and BE-RADIANT, inform the clinical effectiveness evidence submitted by the company. These RCTS provide direct evidence of clinical effectiveness for bimekizumab compared to placebo and three different active comparators (ustekinumab, adalimumab and secukinumab). No head-to head trials are available comparing bimekizumab with the company's chosen cost comparators: risankizumab, brodalumab and ixekizumab. Results of a network meta-analysis (NMA) are therefore included in the CS to provide indirect evidence of clinical similarity between bimekizumab and the company's chosen cost comparators.

3.1.2 Trial design

Trial methodology for BE-READY, BE-VIVID, BE- SURE and BE-RADIANT is summarised in CS section B.3.3.1 and participant flow is described in CS Appendix D.2. All four trials included patients ≥ 18 years old with plaque psoriasis for at least six months prior to screening who were candidates for systemic therapy and/or phototherapy. Patients were required to have moderate to severe plaque psoriasis defined by a PASI score ≥12, affected body surface area (BSA) ≥10% and IGA score ≥3 on a 5-point scale.

All four trials consisted of an initial 16-week treatment period followed by a maintenance period ranging from 32 to 40 weeks. Co-primary endpoints were measured at week 16 and included:

- a PASI 90 response in BE-READY, BE-VIVID, BE- SURE,
- a PASI 100 response in BE-RADIANT and
- for all four trials, an investigator's global assessment response (IGA) 0/1 response (represented by an IGA score of 'clear' (0) or 'almost clear' (1)) with at least a two-category improvement from baseline.

Treatment regimens and comparators differed between the trials as follows:

- **BE-READY** (77 sites; 9 countries): 435 patients were randomised 4:1 to receive **bimekizumab 320 mg every 4 weeks (Q4W)** or **placebo** for 16 weeks. Patients on bimekizumab with a week 16 PASI 90 response entered a 40-week randomised withdrawal phase and were re-randomised 1:1:1 to bimekizumab 320 mg Q4W or bimekizumab 320 mg every 8 weeks (Q8W) or placebo. Patients without a response at week 16 or who relapsed during the withdrawal phase entered an open label bimekizumab 320 mg Q4W 'escape' arm.
- **BE-VIVID** (105 sites; 11 countries): 567 patients were randomised 4:2:1 to receive **bimekizumab 320 mg Q4W, ustekinumab 45/90 mg every 12 weeks (Q12W)** or **placebo** for 16 weeks followed by a 36-week maintenance period. At week 16, patients on placebo switched to bimekizumab 320 mg Q4W.
- **BE-SURE** (77 sites; 10 countries): 478 patients were randomised 1:1:1 to receive **bimekizumab 320 mg Q4W; bimekizumab 320 mg Q4W**, switching to Q8W from Week 16; or **adalimumab 40 mg every 2 weeks (Q2W)**, switching to bimekizumab 320 mg Q4W at Week 24.
- **BE-RADIANT** (77 sites; 11 countries): 743 patients were randomised 1:1 to receive **bimekizumab 320 mg Q4W** or **secukinumab 300mg Q4W**. At Week 16, patients were randomised 1:2 to receive bimekizumab 320 mg Q4W or Q8W. At the end of the 48-week double blind period, patients could enter a 96-week open label extension period.

Patients completing the randomised withdrawal phase or escape arm of BE-READY or the maintenance phase of BE- SURE or BE-VIVID were eligible to take part in a 144-week open-label extension study (BE-BRIGHT) to assess the long-term safety, tolerability and efficacy of bimekizumab. Only safety data from BE-BRIGHT are included as part of a pooled safety evaluation in the current submission. In response to clarification question A7, the company report that final results from BE-BRIGHT are expected in mid-2023 and that interim efficacy and safety results (from a data lock at June 2020) are available on request. Patients not entering BE-BRIGHT had a safety follow up 20 weeks after their final dose in their original trial.

3.1.3 Key efficacy results from pivotal trials

The CS is primarily based on evidence of clinical effectiveness for bimekizumab during the initial 16-week treatment period of the pivotal trials. Key results from these trials are as follows:

- Bimekizumab Q4W achieved [redacted] for the PASI 90 co-primary endpoint at week 16 compared to placebo [redacted] ustekinumab ([redacted]) and adalimumab ([redacted]) in BE-READY, BE-VIVID and BE-SURE (CS Figure 8; all p values <0.001 for superiority).
- Bimekizumab Q4W achieved a [redacted] in BE-RADIANT (co-primary endpoint) compared to secukinumab [redacted] (CS Figure 9; p<0.001 for superiority).
- IGA 0/1 response rates were also higher for bimekizumab Q4W compared to placebo, ustekinumab and adalimumab (p<0.001 for superiority) in BE-READY, BE-VIVID and BE-SURE; [redacted] (CS Section B.3.6.2 and CS Appendix K).

Key results across the four pivotal trials for the less stringent PASI 75 response measure are as follow:

- Bimekizumab Q4W achieved [redacted] response rates at week 16 (ranging from [redacted] to 95.4%) compared to placebo (2.3% to [redacted]%), ustekinumab [redacted] and adalimumab (69.2%), [redacted]).
- The PASI 75 response rate was also higher for bimekizumab Q4W at week 4 (after a single dose) compared to all trial comparators (pre-specified secondary endpoint; all [redacted] for superiority; CS Figure 10).

Key results from the maintenance periods from the bimekizumab trials are as follows:

- Supporting evidence of [redacted]) in BE-VIVID, BE-SURE and BE-RADIANT (CS Figures 12-14).
- A pooled analysis of BE-VIVID, BE-SURE and BE-RADIANT showed that a [redacted] with PASI 90, PASI 100 and IGA 0/1 responses at week 16 maintained the response [redacted] (CS Table 19).

- In BE-READY, the relapse rate (defined as not achieving a PASI 75 response at Week 20 or later) of patients who had a PASI 90 response at week 16 and who entered the randomised withdrawal phase was [redacted] for the bimekizumab Q4W arm and [redacted] for the bimekizumab Q8W arm compared to [redacted] for the placebo arm (CS section B.3.6.3). Time to relapse was not reported.

The ERG notes that results from the trial maintenance periods are not used in the economic modelling or in the NMA. The company consider that the data from the initial 16-week treatment period are most relevant for decision making, in keeping with previous NICE appraisals in this topic area (clarification response A16). They also explain that the different design features during the maintenance periods in the trials across the evidence base (lack of placebo control, different inclusion criteria, different doses etc) would lead to data challenges if an NMA were performed. The ERG agrees that the company's focus on the initial treatment period is consistent with previous NICE appraisals.

Results for other endpoints measured in the trials include PASI 50, symptoms of psoriasis (itch, pain and scaling), scalp IGA, palmoplantar IGA (pp-IGA), modified Nail Psoriasis Severity Index (mNAPSI) and the disease-specific quality of life measure Dermatology Life Quality Index (DLQI) (CS section 3.6.2 and Appendix K).

Pre-specified sub-group analyses for data pooled from BE-READY AND BE-VIVID are included in CS Appendix E for the subgroups listed in the NICE scope. PASI 90, PASI 100 and IGA 0/1 response rates [redacted]

3.2 Critique of the clinical effectiveness evidence submitted

3.2.1 Company searches for clinical evidence

The company's searches for clinical effectiveness evidence were initially performed up to 5th March 2019 and updated on 1st July 2020 (CS Appendices D.1.1 and D.1.2). Studies of all relevant systemic therapies (non-biologic and biologic) were included which is consistent with the NICE scope but broader than the company's decision problem which focuses on selected biologics. The search identified a total of 84 studies for inclusion in a network meta-analysis (see section 3.4 below) including the 4 pivotal phase III RCTs of bimekizumab. The ERG

considers the searches and selection criteria to be appropriate and do not believe any relevant published trials were excluded.

3.2.2 Internal validity of bimekizumab trials

The company assessed the four bimekizumab RCTs as having a low overall risk of bias (CS section B.3.5 and Appendix D.3) according to the NICE quality appraisal checklist. The ERG agrees. Discontinuation rates were generally low at week 16 (around 3-6% of randomised patients, CS Appendix D.2) except in the placebo arms in BE-SURE and BE-VIVID (10-12%). Reported baseline characteristics were well balanced between trial arms with the exception that a [redacted] of patients in the BE-READY placebo arm had [redacted] than in the bimekizumab arm. The ERG's clinical expert is of the opinion that [redacted]

A fixed hierarchical statistical testing sequence was adopted in each of the four trials (CS Table and Appendix I.3). Bimekizumab was tested for superiority against placebo in BE-READY and BE-VIVID for the co-primary endpoints. Testing for superiority against active comparators in BE-VIVID, BE-SURE and BE-RADIANT only proceeded when non-inferiority had been demonstrated for the primary co-endpoints. Planned sample sizes were reached (CS Table 13). The ERG considers the statistical methods to be appropriate.

The ERG consider the trials to be well designed and executed, with overall low risk of bias.

3.2.3 External validity of bimekizumab trials

The majority of patients in the four pivotal bimekizumab trials were Caucasian [redacted], CS Tables 10 and 11 [redacted]. The ERG notes that UK patients represented less than [redacted] of the four trial populations. [1-4]

The mean age (ranging from [redacted]) and BMI ([redacted]) of participants across the four trials were consistent with that observed in a real-world registry of adults with chronic plaque psoriasis treated with biologics in the UK (British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR); CS Figure 6). The trial populations had lower DLQI scores ([redacted]) than patients in the BADBIR register (approximately 17) despite

a slightly higher PASI score ([redacted] compared to approximately 16) and a higher proportion of patients with comorbid psoriatic arthritis ([redacted] compared to approximately 22%). The trial populations also comprised more males ([redacted] than the BADBIR population (around 61%). The ERG's clinical expert considers that the trial populations are relatively similar and any differences are unlikely to impact response.

The trial populations represent a broader population than the company's decision problem (see section 2.1 of this report) and could therefore potentially include patients using bimekizumab as first-line systemic therapy (i.e. naïve to non-biologic systemic therapies), as well as patients previously in receipt of systemic therapy. The proportion of patients who had previously used any systemic therapy ranged from 69.2% to 83.2% and the proportion who had previously used any biologic therapy ranged from 31.1% to 44.4%.

The bimekizumab trial populations were comparable with the trial populations for the company's cost-comparators (risankizumab, ixekizumab and brodalumab) with respect to age, sex and disease duration (CS Appendix D.1.4 Table 11). One exception was the trial population of the SustaIMM phase II/III trial comparing risankizumab and placebo in Japanese patients comprising slightly older patients and a higher proportion of male patients. [5] The proportion of patients who had used prior biologic therapy varied more widely across the cost-comparator trials (7.9% to 46%; CS Appendix D.1.4 Table 11) which may reflect changing practice over time.

3.3 Critique of the evidence on safety submitted by the company

Safety data were pooled from the bimekizumab clinical trial programme as follows:

- Pool S1 included data from the initial treatment period (weeks 0-16) of the placebo-controlled trials, BE-READY and BE-VIVID.
- Pool S2 included data from the initial treatment, maintenance and open-label extension periods for all bimekizumab doses all Phase II and Phase III bimekizumab trials, except BE-RADIANT as this study was still blinded at the time of pooling.

3.3.1 Safety data pooled from all Phase II and Phase III bimekizumab trials

Pooled adverse event frequencies for the bimekizumab arms from trials in Pool S2 (N=[redacted]; CS section B.3.10 and Appendix F) are as follows:

- [redacted]% of patients in Pool S2 reported one or more treatment emergent adverse event (TEAEs).
- The most frequent TEAEs were reported within [redacted]
- [redacted]% of patients had a treatment-related TEAEs (as assessed by investigator); [redacted] was the most frequently reported treatment-related TEAE ([redacted]%).
- Pre-specified AESI were reported [redacted] (CS section 3.10.2).
- [redacted]% of patients reported a serious TEAE and [redacted]% discontinued treatment due to TEAE(s)
- The CS does not report the number of serious TEAEs assessed as related to bimekizumab, however, [redacted].

3.3.2 Comparative safety for bimekizumab versus placebo

Pooled adverse event frequencies for bimekizumab compared to placebo from Pool S1 (N=[redacted]; CS Appendix F) are as follows:

- A [redacted] proportion of patients receiving bimekizumab Q4W experienced one or more TEAE compared to placebo ([redacted]% versus [redacted]% respectively).
- Treatment-related TEAEs were [redacted] in patients receiving bimekizumab Q4W compared to placebo ([redacted]% versus [redacted]%).
- [redacted]
- [redacted] of patients receiving bimekizumab Q4W [redacted] and [redacted] in the bimekizumab Q4W group ([redacted]%) [redacted]

3.3.3 Comparative safety for bimekizumab versus active comparators

Adverse event frequencies for bimekizumab compared with each respective active comparator in BE-VIVID (ustekinumab), BE-SURE (adalimumab) and BE-RADIANT (secukinumab):

- Overall incidences of TEAEs were [redacted] during the initial treatment periods and across both initial treatment and maintenance periods in these three studies (for details see CS Appendix F,11 to F.1.3 Tables 17 to 21).
- [redacted].
- Treatment-related TEAEs were [redacted] in bimekizumab trial arms (ranging from [redacted] compared to respective active comparators (ranging from [redacted]). The CS reports that this is likely driven by a higher frequency of fungal infections in patients receiving bimekizumab. The majority of cases of oral candidiasis across all four pivotal trials were mild to moderate [redacted] managed with standard anti-fungal therapy and did not lead to treatment discontinuation (CS Table 25).

3.3.4 Comparative safety for bimekizumab versus cost comparators

Network meta-analyses were conducted to compare frequencies of serious AEs and AEs leading to treatment discontinuation between bimekizumab and the company's selected cost comparators (CS Figures 18 and 19). The results of these NMAs are further discussed in the next section of this report (section 3.4).

3.4 Critique of the Network Meta-Analysis (NMA) submitted by the company

The pivotal phase III bimekizumab RCTs did not include any of the three biologic drugs selected for cost comparison in the decision problem. Thus, an indirect comparison was required to assess similarity between bimekizumab and these biologics. As we noted earlier, cost-comparison analyses have informed the appraisals of two NICE- recommended biologic drugs in this indication (risankizumab and guselkumab). In both appraisals, the assumption of similarity in efficacy and safety was informed by network meta-analyses (NMA). Likewise, NMA is the company's chosen approach for demonstrating similarity of bimekizumab to existing approved biologic drugs. Where possible we critique their NMA in terms of consistency with NMA assumptions and data considered acceptable in the previous cost-comparison appraisals.

The indirect treatment comparison (NMA) presented in the CS comprises a total of 84 RCTs, identified by the literature search undertaken for the company's systematic review of clinical effectiveness. NMAs are reported for one efficacy outcome measure and two safety measures:

- Efficacy
    - PASI – patients achieving 50%, 75%, 90% and 100% improvement in PASI at 10-16 weeks.
- Safety
    - Serious adverse events (AEs)
    - Discontinuation due to adverse events (AEs)

These outcome measures directly inform the cost comparison analysis (NB. Of the four PASI categories only PASI 75 informs the efficacy analysis). The ERG notes that an NMA of the DLQI outcome was not reported in the CS, despite this outcome being included in the NMAs included in previous appraisals (TA521 guselkumub; TA596 risankizumab). Based on the results of the bimekizumab phase III RCTs and information available from previous appraisals, the ERG's observation is that, based on the DLQI, bimekizumab appears to be as efficacious as the other biologics in terms of health-related quality of life.

3.4.1 Inclusion criteria for the NMA

As mentioned earlier, the inclusion criteria for the company's systematic review of clinical effectiveness, whilst matching the NICE scope, was broader than the decision problem. The evidence network therefore includes studies of biologic drugs and systemic non-biologic drugs (e.g. methotrexate, cyclosporine). The NMA results, however, are presented in accordance with the decision problem (i.e. only comparisons between biologics). The reason for including non-decision problem treatments in the network is not explicitly reported in the CS. The ERG therefore assumes their role is to provide additional evidence to the network to strengthen the relevant comparisons between bimekizumab and the other biologics. We consider these trials provides the network with slightly greater strength in terms of connectivity, with the caveat that this has the potential to increase heterogeneity (see section 3.4.4).

3.4.2 Quality assessment of trials in the NMA

In response to clarification question A8a, the company confirmed they had used the Cochrane Collaboration's Risk of Bias (RoB-2) tool to assess five individual risk of bias domains and an overall risk of bias judgement for each trial in the NMA. (CS Appendix D.1.7). Most studies (69/84) were assessed as having low risk of bias overall (CS section B.3.9.4). No sensitivity analyses were conducted to assess the impact of studies with 'some concerns' (10/84) or high risk of bias (5/84). The company comment that the main driver of bias was missing data (due

to lack of ITT analysis). No narrative is provided in the CS to justify the company's judgments, and it is unclear how the overall judgement of bias for each study was derived from the individual domain assessments. It was not practical for the ERG to perform an independent appraisal of the 84 trials but we consider the company's critical appraisal methods overall to be appropriate.

3.4.3 NMA modelling approaches

The CS reports using two different statistical modelling approaches their NMA, both based on methods recommended by the NICE Decision Support Unit (DSU):

- A Bayesian multinomial likelihood model using a probit link to estimate PASI response (based on NICE DSU Technical Support Documents (TSD) 2,3 and 5).
- A Bayesian logit model to estimate serious AEs and discontinuations due to AEs (based on NICE DSU TSD2).

The Bayesian multinomial probit regression model (we also refer to this as the 'standard model') was used to simultaneously model treatment response across the PASI-50, 75, 90, and 100 categories. The ERG agrees this is the optimal NMA approach for correlated data such as PASI response. Variations to this model were explored in respect of two key assumptions:

1. **Proportional treatment effects.** The standard model retains the same ranking for each treatment across each PASI-response category. Additionally, the company produced a model which relaxed this assumption - the "REZ" multinomial probit model. They suggest that relaxing this assumption is more realistic, less restrictive, and is supported by empirical evidence of modest variability in treatment rankings when separate binomial analyses were conducted for PASI 75, 90 and 100. The company also notes that the REZ model was consistently a better fit compared to the standard multinomial probit model, which may suggest a violation of the proportional treatment effect assumption in the latter. Although the REZ model does not appear to have been used in previous NICE appraisals of biologics for plaque psoriasis, the ERG considers the company's justification for its inclusion in their NMA is reasonable. We encourage the company to fully publish this model in order it can be considered in any future appraisals in this indication.
2. **Baseline risk**. The company suggests that in autoimmune diseases the placebo rate and the relative effect of a treatment versus placebo in a trial are likely to be related, necessitating an adjustment for baseline placebo risk. They note that adjustments have

been included in the NMAs used in the two previous cost comparison appraisals in psoriasis (TA596 risankizumab, TA521 guselkumab). The company's *A priori* preference, therefore, was to adjust for baseline risk.

For PASI response a total of eight models were run, based on different combinations of the above assumptions plus assumptions about whether random effects or a fixed effect applies (Table 1).

Table 1 – Summary of PASI NMA Bayesian multinomial probit modelling assumptions

Model		
Proportional treatment effects	**Baseline risk**	**Effects**
Relaxation of assumption allowed ("REZ model")	Adjusted	Fixed effect
		Random effects (base case)
	Unadjusted	Fixed effect
		Random effects
Standard assumption	Adjusted	Fixed effect
		Random effects
	Unadjusted	Fixed effect
		Random effects

Source: based on CS Table 22.

The best-fitting models, in terms of lowest deviance information criteria (DIC) value, were those which did not adjust for baseline risk (CS Table 22). However, as stated above, the company's preference was to adjust for baseline risk and to maintain consistency with previous cost comparison appraisals (TA521 guselkimab; TA596 risankizumab). Hence, the REZ multinomial probit model adjusted for baseline risk which had the next lowest DIC (i.e. the next best fit) with random effects was chosen as the base case model (indicated in Table 1 by blue shading). The ERG concurs with the company's preference for random effects given the large quantity of studies and thus the increased likelihood of heterogeneity (see section 3.4.4).

Scenario analyses explored various combinations of alternative assumptions about proportional/non-proportional treatment effects, random effects/fixed effect, and unadjusted/non-adjustments for baseline risk.

For the safety NMA the binomial logit models assuming random effects and a fixed effect yielded similar DIC values, respectively. Given the large number of studies included in the network, and

thus the potential for increased heterogeneity, the company opted for random effects in their base case. The ERG agrees that this decision is appropriate.

3.4.4 Heterogeneity assessment

In such a large network of trials there is inevitable heterogeneity, and a potential for an imbalance of the distribution of treatment effect modifiers of most concern in terms of bias. However, the company argues there is no consensus on treatment effect modifiers in plaque psoriasis trials, although prior biologic use has been hypothesised as a treatment effect modifier (clarification question A9).

Expert opinion to the ERG suggests that, in patients who switch biologic treatments, response to subsequent biologic treatments may be lower than the level of response achieved by the initial biologic therapy. The size of the response to a subsequent biologic depends on whether there was non-response to the previous biologic (primary failure – in which case a the patient might switch to a biologic with a different mode of action) or whether response was achieved but lost over time (secondary failure – in which case a patient might switch to a biologic with a different mode of action, or an alternative biologic with similar mode of action).

The company notes that there was no statistical interaction effect in subgroup analysis on prior use of biologics therapy in the bimekizumab phase III RCTs trials. Their view is that, in the absence of evidence to the contra, prior biologic treatment is assumed not to be a treatment effect modifier. The ERG notes that trial subgroup analyses are not statistically powered to identify treatment interactions and therefore a significant treatment-subgroup interaction cannot necessarily be ruled out.

The CS reports that prior use of a biologic use varied between 0% to 39% of patients in the trials included in the NMA. However, this is not fully informative without knowing the mean or median, nor the proportion of patients who had received multiple biologics, nor if trials of certain biologics had higher proportions of patients with prior biologic use (as might be the case for newer treatments). The ERG notes that the proportion of patients in the bimekizumab phase III RCTs who had previously used biologics was in the range 31%-44%, thus at the upper end of the range for the network as a whole.

Given the relatively large number of trials in the network the ERG presumes that meta-regression would have been feasible to explore the impact of prior biologic use and other patient and study characteristics. The company argues that adjustments they made for baseline placebo risk (as described below) account for heterogeneity between the trials to some extent. The ERG notes that, whilst this may be the case, it cannot necessarily be assumed that the risk of bias has been removed. Nonetheless, given that the proportion of patients with prior biologic use in the bimekizumab trials was at the higher end of the range for the network as a whole, and if it is accepted that response to subsequent biologics may not be as high as the initial biologic, then the results of the NMA are not likely to be biased in favour of bimekizumab.

3.4.5 NMA data and statistical procedures

The effect estimates from each trial that were used in the NMA were not reported in the submission, but data formatted for the analysis was provided alongside model programming code following ERG request (clarification question responses A12-14). It was not practical for the ERG to cross-check the data against the 84 source trials for accuracy.

The CS states that data from the intention-to-treat (ITT) population of all included studies informed the NMA. However, the ERG is unclear which, if any, outcome data has been imputed by the company. The CS states "NRI [non-responder imputation] data was used as the preferred imputation method for accounting for missing PASI outcome data" (CS p80). However, clarification question responses A12 and A14 state that the company did not impute any data in the base case REZ model and the baseline risk adjusted models. Further, the data provided for the standard model matches that of REZ model hence the ERG remains unclear what, if any, imputation was made by the company.

The ERG validated the company's standard multinomial probit code against the code in NICE DSU TSD2 and was satisfied the REZ model (which is based on the standard multinomial probit code) had been reasonably implemented. The company used a number of semi-informative priors in the REZ model. These priors did not affect model fit (clarification question response A18) however any impact these may have had on treatment effects is uncertain.

3.4.6 NMA results

[redacted]

The base case results were consistent across the scenario analyses including the REZ fixed effect model (CS Appendix D, Figure 5), models without baseline adjustment (CS Appendix D, figures 6 & 7), and the standard random effects multinomial probit model (CS Appendix D, figure 8).

In the NMA of safety outcomes no statistically significant differences were found between bimekizumab and any of the comparator biologics in terms of serious AEs and discontinuations due to AE (CS, Figures 18, 19).

3.4.7 Consistency of NMA results with other evidence

Parity between bimekizumab and the comparator biologics, as suggested by the results of the NMA, is supported by direct evidence from the bimekizumab trials, NMA results from previous appraisals, and clinical opinion.

As reported earlier (section 3.1) head-to-head comparisons of bimekizumab versus adalimumab, secukinumab, and ustekinumab from the phase III bimekizumab trials showed that bimekizumab had similar or better PASI response rates in relation to these comparators.

Analyses informing previous appraisals have also suggested similar efficacy between biologics. Risankizumab was comparable to guselkumab, and equal or better compared to other biologics across PASI-response categories (TA596). Similarly, guselkumab had comparable (non-statistically significant differences) PASI-90 and PASI-75 responses to those of ixekizumab,

secukinumab, ustekinumab, infliximab, adalimumab, and guselkumab (TA521 committee papers, company submission, Table 14).

The assertion of comparable safety is supported by evidence of a similar safety profile between bimekizumab and comparator biologics in the head-to-head bimekizumab phase III trials (CS Appendix D, tables 17, 19 & 20; section 3.3 of this report). Likewise, similar safety profiles amongst the biologics were reported in the guselkumab and risankizumab appraisals

Expert clinical opinion to the ERG also concurs that the assumption of similar efficacy and safety for bimekizumab is reasonable.

3.4.8 Consistency of placebo efficacy and safety outcomes in biologics trials

The ERG assessed the consistency of the placebo arm PASI response and safety outcomes from the bimekizumab phase III trials with those reported by trials of the other biologics.

CS Appendix D.1.4, Figure 2 shows that the placebo response rate for PASI 75 at the end of the initial treatment period ranged from 0 to 18.9% across the placebo arms of the trials included in the NMA, with most trials reporting a placebo response rate <10%. (NB. The ERG notes that the BE-ABLE study, a phase IIb bimekizumab RCT is included in this Figure but is not included in the NMA). The placebo response rate for PASI 75 ranged from [redacted]% in the bimekizumab trials (BE-READY and BE-VIVID) and [redacted] to that observed in key pivotal trials used to support NICE submissions for the cost comparator drugs (risankizumab: 8.2 to 9.8%; brodalumab: 2.7-8.1%; ixekizumab: 2.4-7.3%). [6-8] Smaller placebo response rates were observed in the bimekizumab trials for PASI 90 ([redacted]) and PASI 100 ([redacted]) and for SAEs [redacted]%) which were [redacted] with those observed for the cost comparator trials. [6-8]Discontinuations due to AEs were [redacted] in the placebo arms of the bimekizumab trials ([redacted]%) compared to the cost comparator trials (ranging from 0.3 to 3.9%). The ERG's conclusion, based on the evidence available, is that the bimekizumab trial placebo efficacy and safety outcomes are not discordant with those of the trials of other biologics for plaque psoriasis.

3.5 ERG conclusions on the clinical effectiveness evidence

- The clinical effectiveness evidence for bimekizumab is from a series of large multinational phase III RCTs. The trials have compared bimekizumab with placebo and three biologic treatments: adaliumumab, ustekinumab and secukinumab. Although these comparator

treatments are still considered standard practice in the management of plaque psoriasis, a number of newer biologic drugs have been recommended by NICE since the trials were initiated.

- The trials appear well designed and executed, with overall low risk of bias. Statistical hypotheses included demonstrating non-inferiority and then superiority of bimekizumab to comparators.
- The bimekizumab trial populations were comparable with the trial populations for the company's cost-comparators (risankizumab, ixekizumab and brodalumab), and appear generalisable to patients treated within the NHS. The bimekizumab trial populations represent a broader population than that defined in the company's decision problem.

- The company's NMA is informed by a comprehensive systematic literature review. The ERG considers the review to be low risk of bias and is unlikely to have omitted any relevant key studies.
- The inclusion criteria for the NMA is broader than the decision problem, and consequently the network includes a proportion of trials of systemic non-biologic treatments. Appropriately, however, the results of comparisons of bimekizumab versus systemic non-biologics are not presented. The ERG's assumption is that trials of systemic non-biologics are included to strengthen connections within the network by increasing the number of patients contributing outcome data. Whilst this might be beneficial for boosting statistical power, a limitation is that it may also increase heterogeneity.
- The NMA modelling approaches are appropriate, based on NICE DSU recommended methodology. Reporting of methodology and statistical procedures is generally good.
- The company's base case NMA model (the REZ model) uses an alternative assumption about proportional treatment effects (i.e. that the ranking of the treatments in probability of PASI response is not necessarily the same across each of the four PASI-response categories) not featured in previous appraisals of biologics in plaque psoriasis. However, the ERG considers the company's justification for this model to be reasonable. The NMA results are consistent across a comprehensive set of scenario analyses, demonstrating robustness to modelling assumptions.
- The ERG notes heterogeneity in some baseline patient characteristics across the trials, particularly prior biologic treatment experience, a hypothesised treatment effect modifier. The CS reports that between 0-39% of patients across the trials had previous biologic experience. A similar proportion of patients in the bimekizumab trials were biologic

experienced. If it is assumed that response to a biologic treatment (in this case bimekizumab) might be lower for patients who had an inadequate response/loss of response to a previous biologic, then, in the ERG's opinion, any bias from heterogeneity in the NMA is not likely to favour bimekizumab.

- Based on the robust results of the company's NMA, and the consistency of these results with those from previous NICE appraisals, the ERG considers the assertion of similarity in efficacy and safety between bimekizumab versus other biologics to be acceptable.

4 Summary of the ERG's critique of cost evidence submitted

4.1 Decision problem for cost comparison

4.1.1 Population

We discuss the company's specification of the population for the decision problem in section 2.1 above. The ERG agrees that the population for the cost-comparison analysis should reflect that in NICE recommendations for the comparators. In practice, the cost analysis uses input parameters estimated from trials with a broader population:

- The modelled cohort has a mean age of 45.1 years, with 69% male (CS Tables 10 and 11), based on the pooled ITT populations of the bimekizumab RCTs BE READY, BE SURE, BE VIVID, and BE RADIANT trials. These demographics are consistent with models for comparator appraisals (TA596 AbbVie submission for risankizumab Table 21; TA511 for brodalumab Leo Pharma submission Table 56; and TA442 for ixekizumab Eli Lilly submission Table 90); and with other trials in the company's NMA (CS Appendix D Table 11). In the model, population demographics only affect mortality rates, which has little impact on cost estimates (CS Table 31).
- The key clinical input in the model (the probability of a PASI-75 response after the initial induction period) comes from the company's base case NMA (CS Appendix D.1.8 Table 13). Limited subgroup analyses by baseline psoriasis severity and prior therapy experience are available for bimekizumab versus placebo from the BE READY and BE VIVID trials (CS Appendix E). This found [redacted].

Similar issues have arisen in previous NICE appraisals, and committees have concluded that the trial populations are generalisable to the target population of NHS patients who meet existing

criteria for access to biologics. For example, see section 3.5 in the brodalumab guidance (TA511) and paragraphs 4.5, 4.6 and 4.8 in the ixekizumab guidance (TA442).

4.1.2 Comparators

The analysis compares bimekizumab with brodalumab, ixekizumab and risankizumab. As stated in section 2.2 above, the ERG considers that these comparators are appropriate for a cost-comparison.

4.2 Cost-comparison model

The company describes their cost-comparison model in CS section B.4.2.1. The model structure is illustrated in CS Figure 20. The model structure and key assumptions are consistent with previous cost-comparisons for risankizumab and guselkumab (TA596 and TA521), and there are shared features with other appraisals of biologics for adults with moderate to severe psoriasis. See CS section B.2 and Table 5 for the company's summary of key clinical features of prior appraisals. See CS Table 27 for a summary of the parameter values in the company's base case and scenario analyses. We discuss these inputs below.

4.3 Model parameters

4.3.1 Induction response

In the base case costing model, the company sets the PASI 75 response probabilities for the included comparators (ixekizumab, risankizumab and brodalumab) equal to the bimekizumab estimate of [redacted] from their preferred NMA analysis [redacted] (CS Appendix D.1.8 Table 13). [redacted] 90.1% (CrI 87.0% to 92.6%); [redacted] 90.0% (CrI 87.2% to 92.2%); [redacted] 88.5% (CrI 85.3% to 91.1[redacted].

[redacted]

It is therefore important to consider the robustness of the NMA, and other factors, such as

pharmacological similarity when judging the appropriateness of the cost-comparison assumption.

The company present sensitivity analysis for the PASI 75 response rate based on the credible interval [redacted] (CS Figures 21-23). We extend this range to further explore uncertainty over this parameter (from [redacted]).

4.3.2 Discontinuation

An equal probability of 20% discontinuation per year was assumed across all the treatment arms. This is consistent with previous cost-comparisons TA596 and TA521. The company vary this rate in sensitivity analysis by -/+ 20% (16% to 20% annual discontinuation). They also test scenarios with discontinuation rates from alternative sources, as in the TA596 risankizumab cost-comparison: Warren et al. 2015 (11%); TA511 (18.7%); and Egeberg et al. 2018 (19%).[9-11]

4.3.3 Mortality

The model uses general population mortality rates, adjusted for the age and sex of the modelled cohort (England and Wales 2017-2019, ONS 2020).

In the brodalumab appraisal (TA511), the committee concluded that adjustment for the increased risk of death in patients with moderate to severe psoriasis was appropriate (UK GPRD study hazard ratio 1.42, 95% confidence interval 1.25 to 1.62). They noted that the increased risk was likely to be related to co-morbid conditions associated with severe plaque psoriasis, and that treating psoriasis would not extend life.

The company test the impact of excluding mortality in scenario analysis (CS Table 31). We also test the impact of including the mortality hazard ratio (1.42) from TA511.

4.3.4 Costs

The company set out the dosing assumptions and list prices for the calculation of acquisition costs for bimekizumab and comparators in CS Table 26. We summarise the key assumptions in Table 2 below.

Table 2 Dosing and list prices for bimekizumab and comparators

Therapy (dose)	Induction		Maintenance (doses per year)	List price per dose
	Duration	Doses		
Bimekizumab (2 x 160 mg)	16 weeks	5	6.5	[redacted]
Brodalumab (1 x 210 mg)	12 weeks	8	26.0	£640
Ixekizumab (1 x 80 mg)	12 weeks	8	13.0	£1,125
Risankizumab (2 x 75 mg)	16 weeks	3	4.3	£3,326

See confidential addendum to ERG report for comparator PAS prices and analyses

The usual maintenance dose for bimekizumab is 320 mg once every 8 weeks. CS Table 2 notes that: [redacted]." In response to clarification question B1, the company further explains that [redacted]

The ERG acknowledges these points. [redacted] For this analysis, we use [redacted] (clarification response question B1 [redacted]

The company exclude administration and monitoring costs from their cost-comparison analysis (see CS B.4.2.3). They note that administration costs were not included in costings for NICE appraisals of other subcutaneously administered biologics, including the comparators brodalumab, ixekizumab and risankizumab. The clinical expert consulted by the ERG, agreed that self-administration of subcutaneous injections with pre-filled pens is simple, and would not differ for bimekizumab and comparators. Administration is supported by NHS resource at the first injection in clinic, and by company provided home delivery and support (or remote consultation by video because of current COVID-19 restrictions). The ERG therefore agrees that there is no need to include treatment administration costs in the cost-comparison.

We also agree with the exclusion of monitoring costs from the cost-comparison. The expert who we consulted noted that monitoring usually consists of an assessment at 12-16 weeks, with 6/12 monthly routine clinic follow-up. However, monitoring tests are not onerous, and do not differ between biologics. Patients who experience a loss of response on maintenance treatment would usually have a clinic review for assessment and consideration for alternative treatment. However, as the rate of discontinuation is assumed to be the same for bimekizumab and comparators, the cost of treatment-switching would be similar, so does not need to be included in the cost model.

The company also excluded costs for treatment of adverse events (CS B.4.2.4). They explain that the NMAs of serious AEs and discontinuation due to AEs found [redacted] (CS B.3.10.2). The company note higher rates of fungal infections with bimekizumab, but argue that these are mostly mild or moderate, with minimal costs. The ERG's clinical expert agreed that biologic treatments for psoriasis are generally well tolerated, and that adverse event rates are unlikely to differ between treatments.

4.4 ERG model checks

The ERG conducted a range of checks on the company's cost-comparison model. This included verification that all input parameters and model results matched the values cited in the CS and, where available, values in published sources. We also inspected formulae in the Markov trace and intermediate calculations ('white box' verification) and checked that changes to input parameters had a plausible impact on results ('black box' verification).

We identified the following minor issues, neither of which affected the results:

- There are small discrepancies in the sum of the number of patients in the health state traces for bimekizumab, ixekizumab and risankizumab: they do not add up to 1. However, these do not impact on the results.
- Errors in cells L89:089; N90; O90; and O91 in Sheet!Mortality Inputs. These were corrected but made no difference in the overall model results (because they do not apply within the modelled time horizon).

4.5 Cost comparison analysis results

The company base case cost comparison results at list prices are presented in CS Table 29 and at PAS price are in CS Table 30. We note, however, that these analyses do not take account of PAS discounts for comparators. Uncertainty over model assumptions was assessed with one-way sensitivity analyses (presented in CS Figures 21-23) and scenario analyses (CS Figure 31).

4.6 ERG analysis

We summarise the results of the company's base case, sensitivity analyses and scenario analyses at list price in Table 3 and Table 4 below. In line with NICE methodological guidance for FTA cost-comparisons, the company did not report a probabilistic sensitivity analysis. All results are therefore deterministic.

In addition to the company's sensitivity and scenario analyses, Table 4 includes the following ERG scenarios:

- A wider range for the PASI 75 response probabilities ([redacted]) to further explore sensitivity to this parameter.
- A 20-year time horizon.
- Mortality multiplier for moderate to severe psoriasis compared with general population (hazard ratio 1.42 from TA511).
- [redacted]

All of these results indicate that bimekizumab is more costly than the comparators when all treatments are costed at list price. We show results with NHS price discounts for bimekizumab and the comparators in a separate confidential addendum to this report.

Table 3 Company's base case results – list price for bimekizumab and comparators

Therapy	Total cost over 10 years	Cost difference: bimekizumab minus comparator
Bimekizumab	[redacted]	
Brodalumab	£65,769.52	[redacted]
Ixekizumab	£62,304.35	[redacted]
Risankizumab	£62,384.76	[redacted]

Source: Results produced by ERG from the company's model.

Table 4 Company's sensitivity and scenario analyses – list price for bimekizumab and comparators

Scenario		Cost difference: bimekizumab minus comparator		
		Brodalumab	Ixekizumab	Risankizumab
Base case		[redacted]	[redacted]	[redacted]
PASI 75 response (*base case* [redacted])	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted] (lower CrI)	[redacted]	[redacted]	[redacted]
	[redacted] (upper CrI)	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation (*base case 20%*)	11% (Warren 2015)[11]	[redacted]	[redacted]	[redacted]
	16% (-20%)	[redacted]	[redacted]	[redacted]
	18.7% (TA511)	[redacted]	[redacted]	[redacted]
	19% (Egeberg 2018)[9]	[redacted]	[redacted]	[redacted]
	24% (+20%)	[redacted]	[redacted]	[redacted]
Time horizon (*base case 10 years*)	5 years	[redacted]	[redacted]	[redacted]
	20 years	[redacted]	[redacted]	[redacted]
Discount rate (0%)	3.5% per year	[redacted]	[redacted]	[redacted]
Mortality *(base case general population)*	Exclude mortality	[redacted]	[redacted]	[redacted]
	Multiplier 1.42 (TA511)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Results produced by ERG from the company's model.

[redacted]

4.7 ERG conclusions on cost comparison

- The structure and key assumptions of the company's cost-comparison model are appropriate, and consistent with previous cost-comparison appraisals (risankizumab TA596 and guselkumab TA521) and with economic analyses in other appraisals (ixekizumab TA442 and brodalumab TA511). We did not identify any important errors in the model coding.
- Results of the company's NMA suggest that [redacted]. This supports the assumption of similar efficacy, although this may over-estimate costs for the comparators. It is therefore important to consider the robustness of the NMA, and other factors, such as pharmacological similarity when judging the appropriateness of the cost-comparison assumption.
- With list prices for all treatments, bimekizumab is estimated to be more costly than the comparators risankizumab, ixekizumab and brodalumab. This applies for the company's base case analysis and for all company and ERG sensitivity and scenario analyses. Results with PAS discounts for bimekizumab and comparators are shown in a confidential addendum to this report.
- The cost difference between bimekizumab and comparators is most sensitive to assumptions about the rate of discontinuation from maintenance treatment and [redacted]. Results are insensitive to the probability that patients have a PASI reduction of at least 75% over the induction period, when the same probability is assumed for bimekizumab and comparators.

5 ERG commentary on the robustness of evidence submitted by the company

5.1 Strengths

- The ERG considers the phase III bimekizumab trials to be well designed and executed, with low risk of bias. The patient populations in the trials, overall, appear to be representative of patients typically seen in practice in the NHS.

- The company's indirect comparison of bimekizumab to its chosen cost comparators is based on standard NICE DSU methodology, with comprehensive scenario analyses to explore the use of different assumptions around proportional treatment effects and baseline risk. The ERG concurs with the company's assumptions and choice of modelling methods.
- The structure and key assumptions of the company's cost-comparison model are appropriate, and consistent with previous cost-comparisons (risankizumab TA596 and guselkumab TA521) and cost-effectiveness analyses for other comparators (ixekizumab TA442 and brodalumab TA511).
- Results of the company's NMA supports the assumption of similar efficacy for bimekizumab and comparators is required for the cost-comparison.

5.2 Weaknesses and areas of uncertainty

- There is apparent heterogeneity in the NMA in terms of the proportion of patients in the trials who had previously received biologic therapy, a potential treatment effect modifier. However, the ERG does not consider that this biases in favour of bimekizumab.
- Based on list prices for all treatments, bimekizumab is more costly than the comparators risankizumab, ixekizumab and brodalumab. This applies to the company's base case analysis and for all company and ERG sensitivity and scenario analyses. Results based on PAS discounts for bimekizumab and comparators are shown in a confidential addendum to this report.
- The cost difference between bimekizumab and comparators is most sensitive to assumptions about the rate of discontinuation from maintenance treatment and [redacted].

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