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Bimekizumab for treating active psoriatic arthritis

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The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

David Scott critically appraised the clinical effectiveness systematic review, and drafted the report; Karen Pickett critically appraised the clinical effectiveness systematic review, and drafted the report; Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Fay Chinnery critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Joanna Picot critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

Confidential information

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse event
AIC	Academic in confidence
b/tsDMARD	Biological/targeted synthetic disease-modifying anti-rheumatic drug
bDMARD	Biological disease-modifying anti-rheumatic drug
bDMARD-IR	Biological disease-modifying anti-rheumatic drug inadequate responders
BKZ	Bimekizumab
BSA	Body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CCP	Cyclic citrullinated peptide
cDMARD	Conventional disease-modifying anti-rheumatic drug
CI	Confidence interval
CIC	Commercial in confidence
CS	Company submission
DIC	Deviance information criterion
DMARD	Disease-modifying anti-rheumatic drug
DSU	Decision Support Unit
EAG	External Assessment Group
HAQ-DI	Health Assessment Questionnaire – Disability Index
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IL-17A	Interleukin-17A
IL-17F	Interleukin-17F
IL-17AF	Interleukin-17AF
IXE	Ixekizumab
JAGS	Just Another Gibbs Sampler
JAKi	Janus kinase inhibitor
MDA	Minimal disease activity
MHRA	Medicines and Healthcare products Regulatory Agency
mNAPSI	Modified nail psoriasis severity index
MTX	Methotrexate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network meta-analysis
OLE	Open-label extension
OR	Odds ratio
PAS	Patient access scheme
PASI	Psoriasis Area and Severity Index
PATT	Proportionate approach to technology appraisals
PhGA	Physician’s Global Assessment
PBO	Placebo
PGA	Patient’s Global Assessment
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PSO	Psoriasis
QXW	Every X weeks (where X is a number)

Abbreviation	Definition
RCT	Randomised controlled trial
RR	Relative risk
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36 PCS	Short Form-36 Physical Component Summary
SJC	Swollen joint count
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
TA	Technology appraisal
TJC	Tender joint count
TNF	Tumour necrosis factor alpha
TNFi	Tumour necrosis factor alpha inhibitor
TNFi-CI	Tumour necrosis factor alpha inhibitor-contra indicated
TNFi-IR	Tumour necrosis factor alpha inhibitor-inadequate responder or intolerant to prior TNFi therapy
TSD	Technical support document
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drug
UK	United Kingdom
VAS	Visual analogue scale
VLDA	Very low disease activity

1 EXECUTIVE SUMMARY

The company, UCB Pharma, submitted evidence to NICE for bimekizumab in the treatment of people with active psoriatic arthritis, to be considered under NICE's proportionate approach to technology appraisals (PATT) streamlined cost-comparison process.

This summary provides a brief overview of the issues identified by the external assessment group (EAG) as being potentially important for decision making. All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Summary of the EAG's view of the company's cost-comparison case

- The descriptions of active psoriatic arthritis (PsA) and the clinical treatment pathway presented in the company's submission (CS) are appropriate.
- The technology being appraised is bimekizumab, an interleukin-17A (IL-17A), interleukin-17F (IL-17F) and interleukin-17AF (IL-17AF) inhibitor. Bimekizumab has an existing licensed indication for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Regulatory approval is expected in [redacted] for the indication relevant to this cost-comparison, for bimekizumab alone or in combination with methotrexate for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). The company is seeking a positive recommendation from NICE for "*Adult patients with active psoriatic arthritis whose disease has not responded well enough to DMARDs or who cannot tolerate them, and only if the patient has: Peripheral arthritis with three or more tender joints and three or more swollen joints, and i) they have had two conventional DMARDs and at least one biological DMARD, or ii) tumour necrosis factor inhibitors (TNFi) are contraindicated but would otherwise be considered (as described in NICE's technology appraisal guidance on etanercept, infliximab, and adalimumab for the treatment of psoriatic arthritis*[1]" (CS Table 1). This is a narrower population than described in the NICE scope (adults with active psoriatic arthritis) and narrower than the eligible population in the proposed marketing authorisation for psoriatic arthritis. The company's proposed positioning is, however, in the same population for which NICE recommended ixekizumab (an IL-17A inhibitor and the company's chosen comparator) in TA537.
- The NICE criteria for selecting a comparator for a cost-comparison case are that the selected comparator should adequately represent the NICE recommended

treatments as a whole and should have a substantial market share. According to the company, the company's selected comparator ixekizumab has a market share of [redacted] in biological/targeted synthetic DMARD-experienced patients and an estimated market share of [redacted] in TNFi-CI patients and the EAG agrees that the choice of ixekizumab as the comparator in the company's cost-comparison meets NICE's criteria. The EAG's clinical expert also agreed that ixekizumab was the most appropriate comparator for a cost-comparison with bimekizumab.

1.2 The decision problem: summary of the EAG's critique

- The EAG agrees that the company's decision problem seems appropriate.
- The CS does not provide any information on the subgroups to be considered that were listed in the NICE scope (the reason for previous treatment failure, mechanism of action or number of previous treatments, presence or severity of concomitant psoriasis, presence or severity of axial involvement).

1.3 The clinical effectiveness evidence: summary of the EAG's critique

- All the relevant trials are included in the CS. No head-to-head trials of bimekizumab and ixekizumab have been undertaken so the assumption of clinical equivalence is based on the results from network meta-analyses (NMAs).
- The company's key phase 3 RCTs (BE COMPLETE and BE OPTIMAL) and their phase 2 trial (BE ACTIVE) do not appear to fully represent the decision problem populations. The main reasons for this are that it is unclear if trial participants had previously received two cDMARDs or had a contra-indication to TNF-inhibitors. We do not consider this to be a critical issue that would prevent this topic proceeding as a cost-comparison case.
- Two populations were defined for separate NMA networks:
  - a tumour necrosis factor inhibitor (TNFi) experienced population (representing the company's decision problem population of patients who have had two conventional DMARDs and at least one biological DMARD)
  - a TNFi contra-indicated population (representing the company's decision problem population of patients for whom TNFi are contraindicated but would otherwise be considered).
- For safety outcomes, a pooled population of TNFi-experienced and biological/targeted synthetic DMARD-naïve patients was used in an NMA because the safety profiles of the interventions were not expected to differ by treatment experience. The NMAs include more comparators than required for the cost-comparison because they were conducted from a global perspective but because the

majority of included RCTs were comparisons with placebo this is expected to have little impact on the indirect comparison between bimekizumab and ixekizumab.

- The company included all the previously considered key clinical efficacy outcomes from the ixekizumab appraisal TA537: American College of Rheumatology (ACR) 20/50/70, psoriasis area severity index (PASI) 75/90/100, psoriatic arthritis response criteria (PsARC), Minimal disease activity (MDA), Health Assessment Questionnaire – Disability Index (HADQ-DI), enthesitis resolution, dactylitis resolution, pain visual analogue scale (VAS), serious adverse events, discontinuation, and discontinuation due to adverse events. Of these, only two (PsARC and discontinuation) inform the cost-comparison model.
- The NMA was appropriately conducted.
- There was a statistically significant difference in favour of bimekizumab 160mg versus ixekizumab 80 mg Q4W for the efficacy outcomes ACR20, PASI100, PsARC and enthesitis resolution in the TNFi-experienced population and a statistically significant difference in favour of bimekizumab for the ACR70 and PsARC outcomes in the TNFi-CI population. For the remaining efficacy and the HRQoL outcomes there were no statistically significant differences between bimekizumab and ixekizumab (point estimates mostly favoured bimekizumab but credible intervals were typically wide or very wide). For the safety outcomes in the pooled population of TNFi-experienced and biological/targeted synthetic-DMARD naïve patients there were no statistically significant differences between bimekizumab and ixekizumab but the number of events was small and confidence intervals were wide. The EAG notes that for all the outcomes where there was an absence of statistical significance, this does not necessarily imply clinical equivalence between the treatments.
- The EAG does not believe that there are any critical issues in the clinical effectiveness evidence that affect the robustness of the company's case for a cost-comparison.

1.4 The cost-effectiveness evidence: summary of the EAG's critique

- The company conducted a cost-comparison analysis of bimekizumab compared with ixekizumab for the treatment of adult patients with psoriatic arthritis.
- The EAG considers the structure and assumptions of the company's cost-comparison model to be appropriate and consistent with previous cost-comparison appraisals (such as risankizumab TA803 for psoriatic arthritis;[2] bimekizumab TA723 for plaque psoriasis [3]).

- The company's original model included a minor error in the cost of the ixekizumab loading dose, which the company corrected in a new version of the model.
- The assumption that bimekizumab and ixekizumab have similar clinical efficacy (as measured by ACR, PASI and PsARC scores) is based on findings of statistical significance in the company's NMA results.
- The company's cost-comparison analyses are based on PsARC response. The EAG notes that bimekizumab is statistically superior to ixekizumab using this measure; assuming patients respond to both treatments equally may over-estimate the treatment cost of ixekizumab.
- When using list prices for both treatments, bimekizumab is estimated to be more costly than ixekizumab. This applies for the company's base case analysis and for all company and EAG scenario analyses. Results with PAS discounts for bimekizumab and ixekizumab are shown in a confidential addendum to this report.
- The cost difference between bimekizumab and ixekizumab is most sensitive to using a five year time horizon in the model, and also to varying the proportion of patients with psoriatic arthritis and concomitant psoriasis. Results are insensitive to applying the standardised mortality ratio for psoriatic arthritis versus the general population or not.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from UCB Pharma on the clinical effectiveness and cost effectiveness of bimekizumab for treating psoriatic arthritis. It identifies the strengths and weaknesses of the CS. A clinical expert was consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 8th June 2023. A response from the company via NICE was received by the EAG on 16th June 2023 and this is available in the NICE committee papers for this appraisal.

The NICE methodological guidance states that a cost-comparison case may be made if an intervention provides similar or better health outcomes at a similar or lower cost than a comparator intervention.[4] The company has selected ixekizumab as their comparator for the cost-comparison and use a network meta-analysis approach to provide indirect evidence of clinical similarity between bimekizumab and ixekizumab. We agree that the cost-comparison approach is appropriate.

2.2 Background

2.2.1 Background information on active psoriatic arthritis and the treatment pathway

The company has provided an acceptable description of active psoriatic arthritis in the CS (CS section B.1.3.1). The British Society for Rheumatology 2022 guideline for the treatment of psoriatic arthritis defines active peripheral psoriatic arthritis as people having "*at least three tender and three swollen joints or those with fewer joints and either poor prognostic markers or severe disease impact*" (Tucker *et al.*, p. e258).[5] In the CS, the company focuses on a population of people that meet the 2022 guideline definition of active peripheral arthritis (those who have psoriatic arthritis with ≥3 tender joints and ≥3 swollen joints, referred to within the remainder of this report as people with active psoriatic arthritis). Additionally, the company focuses on those who have been treated with two conventional disease-modifying anti-rheumatic drugs (cDMARDs). This is because NICE recommends biologic disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs) only after two cDMARDs (used either solely or in combination with each other) in people with active psoriatic arthritis (CS section B.1.3.3).

The company outline the clinical pathway of care for people with active psoriatic arthritis who have been treated with two cDMARDs in CS section B.1.3.3 and CS Figure 1. The pathway depicted accurately reflects NICE's recommendations for the use of the comparator drugs specified in the NICE scope that are approved treatments for this population.[1; 6-15] Our clinical expert also agreed with the company's description of the clinical pathway.

The company is positioning bimekizumab for the treatment of patients with active psoriatic arthritis who have been treated with two cDMARDs who either:

- are biologic-experienced (that is, have had at least one bDMARD) or
- who cannot receive a TNFi as it is contraindicated

The EAG notes that, as the company describes at the end of CS section B.1.1, terminology has evolved with the advent of new classes of treatments. The company's definition of bDMARD appears to include the tsDMARDS, i.e. the Janus kinase inhibitors (JAKis) tofacitinib and upadacitinib, as well as bDMARDs (CS Figure 1) and in some sections of the CS this group of patients is referred to as b/tsDMARD-experienced. The EAG's clinical expert agreed with the company's proposed use of bimekizumab in the treatment pathway.

The CS states that bimekizumab does not yet have a marketing authorisation for active psoriatic arthritis (see CS Table 2 for details). Bimekizumab is expected to be licensed for use either alone or in combination with methotrexate for the treatment of adults who have active psoriatic arthritis and who have had an inadequate response or who have been intolerant to one or more DMARDs (CS Table 2). Thus, the company's intended positioning of bimekizumab in the care pathway is narrower than the anticipated licensed indication population.

2.2.2 Background information on bimekizumab

Bimekizumab is a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind to specific target molecules in the body. Bimekizumab binds to the immune system messenger molecules called interleukin IL-17A, IL-17F and IL-17AF preventing their interaction with their receptors in the body and thus reducing inflammation.[16] Bimekizumab is currently licensed as a treatment for moderate to severe plaque psoriasis in adults who are eligible for systemic therapy.[17]

Of the NICE recommended treatments for the population of patients with active psoriatic arthritis who have been treated with two cDMARDs (as listed in CS Figure 1), the mechanism of action of bimekizumab is most similar to the monoclonal antibodies ixekizumab and secukinumab, which both block the action of interleukin 17A.[18; 19] Our clinical

expert confirmed that bimekizumab, ixekizumab and secukinumab are pharmacologically similar and that there are no other NICE-approved treatments for active psoriatic arthritis that have a similar mechanism to bimekizumab. The CS states that bimekizumab is as effective as ixekizumab at blocking IL-17A, but more effective than secukinumab at doing the same (CS Table 1). The clinical expert consulted by the EAG said that in theory there may be advantages in bimekizumab's additional targeting of IL-17F and IL-AF, but there are no data available on this.

3 CRITIQUE OF DECISION PROBLEM IN THE COMPANY'S SUBMISSION

CS Table 1 and CS section B.1.1 summarises the decision problem addressed by the company in relation to the final scope issued by NICE. Here we provide our critique of the company's decision problem focusing particularly on the company's deviations from the NICE scope and the company's stated reasons for these.

3.1 Population

The company's decision problem population is narrower than both the population described in the final NICE scope for this appraisal and the population eligible to receive the company's chosen comparator ixekizumab.[20] It is also narrower than the proposed licensed indication for bimekizumab (CS Appendix C). The company's rationale for their decision problem population is that it takes into account the availability of the biosimilar adalimumab (which was not available at the time of the ixekizumab appraisal (TA537)[20]) which means that non-biosimilars are not expected to be used at first-line, except for patients with a contraindication to TNFi. Our clinical expert confirmed that because the biosimilar adalimumab is so much cheaper and is also able to treat other extra-articular manifestations of psoriatic arthritis e.g. iritis, uveitis and inflammatory gut issues, treatments such as ixekizumab and other IL-17 inhibitors are not going to be used as a first-line treatment unless the biosimilar adalimumab cannot be used. The company has therefore aligned their decision problem population with those in NICE recommendations from two technology appraisals that have taken place since the biosimilar adalimumab has been available (TA768, upadacitinib and TA815, guselkumab). The EAG agrees that the company's decision problem population is appropriate. The EAG notes that the populations enrolled in the company's key phase 3 RCTs (described in CS Tables 7 and 9) do not fully represent the decision problem populations (see Figure 1 and section 4.3.7 of this report for additional information).

3.2 Intervention

The company's decision problem applies to bimekizumab, which is both an IL-17A inhibitor and an IL-17F inhibitor (CS Table 2). In the company's key clinical trials bimekizumab is compared to placebo (section 4.3 of this report). The EAG notes that bimekizumab is indicated either alone or in combination with methotrexate, as stated in CS sections B.1.1 and B.1.3.3, CS Table 2 and as described in CS Appendix C. However, the decision problem does not state what proportion of the decision problem population would be expected to receive bimekizumab as monotherapy or in combination with methotrexate. The

EAG observes that CS Appendix J Table 4 reports methotrexate use at baseline in the company's two phase 3 RCT trial populations, BE COMPLETE (43% overall) and BE OPTIMAL (58% overall) trial populations. Concomitant methotrexate use in the company's phase 2 RCT, BE ACTIVE was 64% overall[21] (this includes trial arms receiving bimekizumab doses not relevant to the current appraisal). Our clinical expert's view was that, in the population of people with active psoriatic arthritis in England who would be eligible for bimekizumab, the proportion receiving methotrexate would be similar to that observed in the bimekizumab clinical trials at the start of combination treatment. But, over time this proportion was likely to reduce for clinical reasons (e.g. liver abnormalities) and patient preference for monotherapy if they are in remission.

3.3 Comparator

The NICE scope listed a large number of comparators across six potential subpopulations of patients. From the listed comparators, the company has selected ixekizumab as their comparator of interest and list the reasons why they believe ixekizumab is the most relevant comparator in CS Table 1 (summarised below in section 5.1.1). Ixekizumab is an IL-17A inhibitor, and, according to the company (CS Table 1), it has a market share of [redacted] in b/tsDMARD-experienced patients and an estimated market share of [redacted] in TNFi-CI patients. Ixekizumab is administered by subcutaneous injection (SC), as is bimekizumab, but requires an initial loading dose which bimekizumab does not. The EAG's clinical expert agreed that this was the most appropriate comparator for a cost-comparison with bimekizumab.

There are three key phase 3 RCT trials for ixekizumab:

- SPIRIT-P1[22] (ixekizumab versus placebo but also including an adalimumab active reference arm)
- SPIRIT-P2,[23] (ixekizumab at two different dose frequencies versus placebo)
- SPIRIT-H2H[24] (ixekizumab versus adalimumab) which is only included in the NMA for safety outcomes.

SPIRIT-P1 and SPIRIT-P2 are both included in the company's NMAs for effectiveness, SPIRIT-P2 is included in the NMA for HRQoL and all three studies are included in the NMA for safety outcomes.

In the ixekizumab RCTs, concomitant methotrexate use was 54%, 41% and 59% respectively. Therefore, in the NMA that allows comparison of bimekizumab and ixekizumab, there are similar proportions of patients in the three ixekizumab RCTs receiving concomitant methotrexate as in the three bimekizumab RCTs (range 43% to 64% across the

three trial populations). Because the use of concomitant methotrexate is similar for the intervention bimekizumab and the selected comparator ixekizumab, the costs for methotrexate should balance out. The EAG's clinical expert confirmed that they would expect the proportion of patients receiving concomitant methotrexate to be the same for patients eligible for bimekizumb and those eligible for ixekizumab. Therefore, it is appropriate that concomitant methotrexate is not included in the cost-comparison.

3.4 Outcomes

CS Table 1 lists the full range disease activity and other outcomes reported in the CS that align with the outcomes specified in the NICE scope. The EAG considers the range of trial outcomes reported for the bimekizumab RCTs are appropriate and consistent with the outcomes reported for the comparator trials.

The EAG notes that the outcomes which contribute data to the cost-comparison base-case analysis, and which were deemed influential clinical effectiveness parameters in the model for the ixekizumab (TA537) appraisal, are:

- the Psoriatic Arthritis Response Criteria (PsARC) (this is a measure of disease activity defined in section 4.3.6 of this report and used in the cost comparison model as described in section 5.1.3.1 of this report)
- the annual treatment discontinuation rate (in the current cost-comparison an assumed value for this rate is used, which is consistent with previous technology appraisals as described in section 5.1.3.2 of this report).

This EAG report will therefore focus on the PsARC and annual discontinuation rate when reporting outcomes from the key clinical trials and the NMA.

Although deaths are included in the company's reporting of adverse events, the company does not include mortality derived from its RCTs in the cost comparison. The EAG is aware that the earliest technology assessment for psoriatic arthritis, TA199[1] (etanercept, infliximab and adalimumab) included a standardised mortality ratio (SMR) for psoriatic arthritis versus the general population of 1.65 for men and 1.59 for women. Over time, data has shown that excess mortality has declined, meaning that the SMR used in more recent appraisals, including that of ixekizumab (TA537[10]), was lower at 1.05. Typically, the assumption has been that mortality does not vary by treatment. In the cost-comparison of risankizumab for psoriatic arthritis (TA803[25]), risankizumab and guselkumab were assumed to be clinically equivalent in their effect on mortality. For this current cost-comparison of bimekizumab, bimekizumab and ixekizumab are assumed to clinically equivalent in their effect on mortality

and an SMR of 1.05 is used which the EAG views as appropriate (see section 5.1.3.3 of this report).

3.5 Subgroups to be considered

CS Table 1, under 'Subgroups to be considered', states that there were 'None specified' in the final scope issued by NICE, but this is not the case. The NICE scope under the section 'Other considerations' states:

- If evidence allows the following subgroups will be considered:
  - the reason for previous treatment failure (for example due to lack of efficacy, intolerance or adverse events)
  - mechanism of action or number of previous treatments
  - presence or severity of concomitant psoriasis (no psoriasis, mild, moderate or severe psoriasis)
  - presence or severity of axial involvement

The CS does not present data on any of these subgroups that are specified in the NICE scope (CS section B.3.7 on subgroup analysis states 'not applicable' and no data are presented).

The company state in CS Table 1 that they have presented data in the CS for the following two sub-populations, to align with the decision problem population (and thus the proposed positioning of bimekizumab in the clinical pathway):

- those who are tumour necrosis factor alpha inhibitor-contraindicated (TNFi-CI)
- those who are biological DMARD inadequate responders (bDMARD-IR).

We note that CS Table 1 is the only place in the CS where the company describe a population who are biological DMARD inadequate responders. We assume that this population is equivalent to the b/ts DMARD-experienced population that is described in the remainder of the CS.

We critique in section 4.3 how well the populations of the pivotal bimekizumab trials map onto these decision problem sub-populations.

At the end of CS section B.1.1 the company explains how the terminology used to describe the population subgroups of interest differs between sections of the CS and provide some insight into how descriptions have changed over time in response to the introduction of new classes of treatment. For example, trials that were designed when the only type of biologic

treatments available were TNF inhibitors refer to patients either as being TNFi-naïve or TNFi-experienced. However, in recent clinical guidelines patients are referred to as b/tsDMARD-experienced or b/tsDMARD-naïve, which reflects the availability of a wider range of treatment options and choice of first-line therapy. We have summarised the company's use of terminology in different sections of the CS for the treatment-naïve and treatment-experienced patient subgroups in Figure 1 which provides an indication of how the different populations nest together.

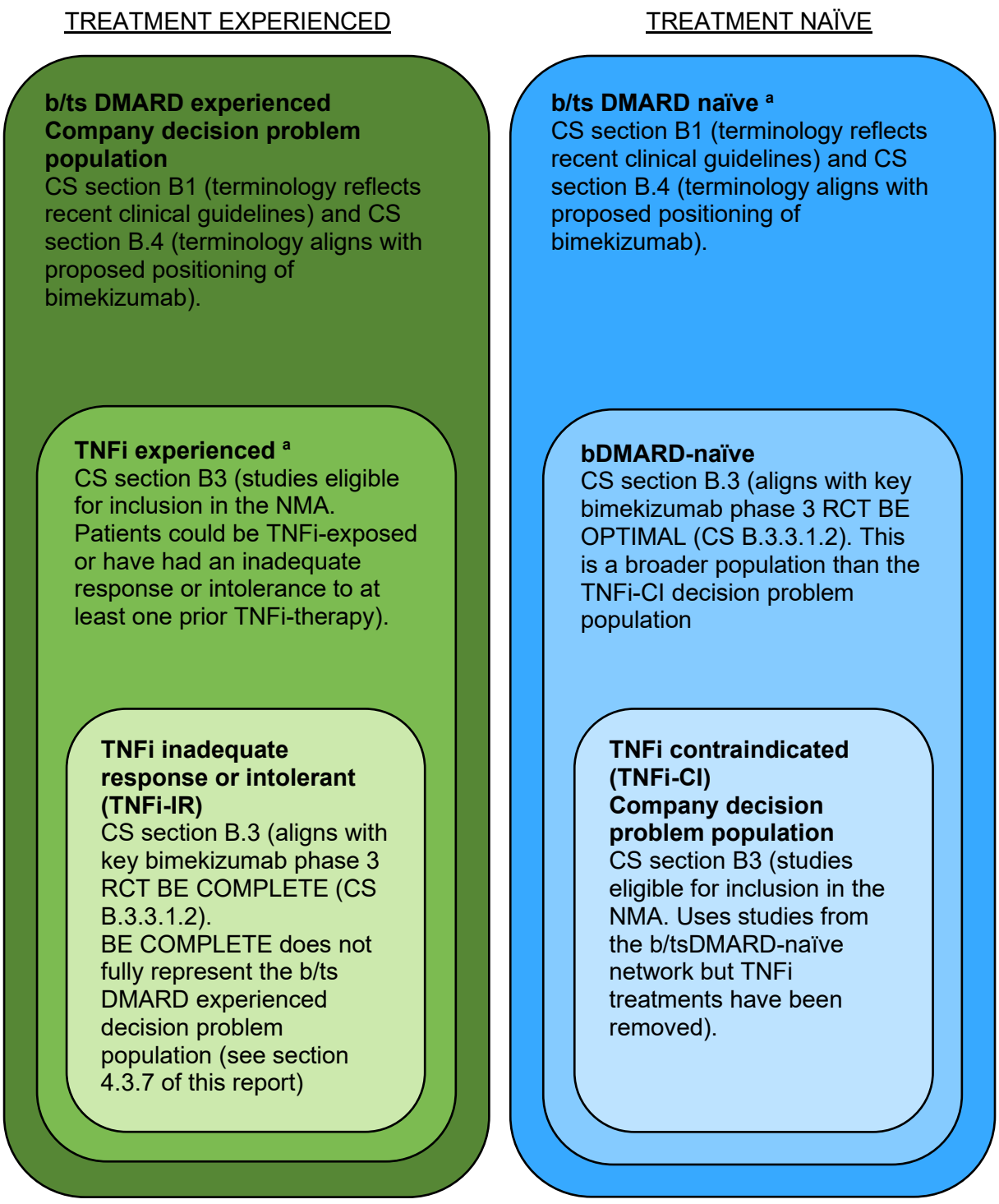

Figure 1 Terminology used to describe different population subgroups in the CS

Source: Figure drawn by the EAG based on text within CS section B.1.1
bDMARD, biological disease-modifying anti-rheumatic drug; b/ts DMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; TNFi, tumour necrosis factor alpha inhibitor; TNFi CI, tumour necrosis factor alpha contra-indicated; TNFi IR, tumour necrosis factor alpha inadequate responders (within the BE COMPLETE RCT, tumour necrosis factor alpha intolerant was also included under the TNFi IR abbreviation)
[a] The NMA also includes a population, described as a mixed population, that includes patients who are b/tsDMARD-naïve or TNFi-experienced.

4 EAG'S CRITIQUE OF THE CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

4.1 Critique of the company's systematic review methods

The company carried out a systematic literature review to identify relevant clinical effectiveness evidence, searching for RCTs only (CS Appendix D). Searches were initially performed from 1991 up to 3rd December 2015 in an original version of the review, which was then updated three times, with the final searches performed on 1st January 2023 (CS Appendix D.1.1). Studies of a range of therapeutic interventions for psoriatic arthritis were searched for and eligible for the review (see CS Appendices D.1.3 and D.1.4). Thus, the review's scope was broader than the company's decision problem, which focuses on bimekizumab as the intervention and ixekizumab as the chosen comparator (CS Table 1). The population eligibility criteria were broader than the population specified in the company decision problem (see CS Appendix D.1.4 Tables 20, 21, CS Appendix D.1.5 Table 22 and CS Table 1), but would have identified studies relevant to the decision problem. The EAG considers that overall the searches, search sources and study selection criteria were appropriate. Generally, the review and all the updates of it were well conducted, but it is unclear how many reviewers carried out the critical appraisals of the included studies and if they did so independently, resulting in uncertainty about the reliability of the company's critical appraisals. It is unlikely that any relevant studies would have been missed.

Overall, the review included 66 RCTs (reported in 540 publications) that met the broad inclusion criteria (CS Appendix Figure 23). Three were of bimekizumab (CS Appendix Table 23). In addition to these three RCTs, two studies providing long-term follow-up data to two of the bimekizumab RCTs are also reported in the CS (CS section B.3.2), but it is unclear how they were identified and critical appraisals were not included for these (CS Appendix D Table 41).

4.2 Overview of the clinical effectiveness evidence submitted by the company

The company includes the following phase 3 RCTs of the clinical efficacy of bimekizumab versus placebo in adults with adult-onset, active psoriatic arthritis, as primary evidence in the CS (CS section B.3.2):

- **BE COMPLETE** (PA0011; NCT0389658)[26] – the patient population included in this RCT had either had an inadequate response, or were intolerant, to one or two tumour necrosis factor inhibitor (TNFi) therapies for either psoriatic arthritis or psoriasis (CS Table 7).

- **BE OPTIMAL** (PA0010; NCT03895203)[27] – the population included in this RCT were treatment-naïve to biologics for either psoriatic arthritis or psoriasis (CS Table 7).

A third study, **BE VITAL** (PA0012; NCT04009499),[28] which does not appear to have been identified by the SLR, was also included. This is an ongoing open-label extension to BE COMPLETE and BE OPTIMAL (CS section B.3.2). The CS states that, currently, this study only provides follow-up data for BE COMPLETE from the end of the 16-week RCT to Week 52.

The company also included the following phase 2 RCT of bimekizumab versus placebo in adults with adult-onset, active psoriatic arthritis, and its open-label extension (OLE) study, as supportive evidence to demonstrate long-term efficacy and safety up to three years (CS Table 8):

- **BE ACTIVE** (PA0008; NCT02969525)[21] – the population included in this RCT were either TNFi-naïve or were TNFi-experienced but had inadequately responded to, an intolerance of, or lost access to the TNFi treatment.
- **BE ACTIVE 2** (PA0009; NCT03347110)[29] – the population included in this study had completed the BE ACTIVE trial (i.e. those who had not met withdrawal criteria). This study does not appear to have been identified by the SLR.

An NMA was also included in the submission to assess the relative efficacy and safety of bimekizumab versus a range of treatments for psoriatic arthritis, including ixekizumab (CS section B.3.9). Only the results of the bimekizumab versus ixekizumab comparison are relevant to this appraisal. We critique the NMA in section 4.5 of this report.

4.3 Description of the pivotal studies of bimekizumab

4.3.1 BE COMPLETE

The methodology of the BE COMPLETE RCT is summarised in CS sections B.3.2.1, B.3.3.1.1.1, B.3.3.1.2, B.3.3.1.3 and Appendix J, and the participant flow through the trial is shown in CS Appendix D.2 Figure 3. The statistical analysis of the RCT is described in CS section B.3.4. BE COMPLETE was a phase 3 RCT comparing bimekizumab 160 mg against placebo, both administered every four weeks (Q4W) by SC injection, in the treatment of active psoriatic arthritis over a 16-week treatment period (CS Table 7 and CS section B.3.3.1) in 400 randomised participants (CS Appendix D.2 Figure 3). The trial used the expected licensed dose of bimekizumab (CS Appendix C). At the end of the trial, participants who completed Week 16 assessments could enter the BE VITAL OLE. For those who did

not enter this study, there was a safety follow up visit 20 weeks after the last dose of the study drug (CS section B.3.3.1). Permitted concomitant medication in the BE COMPLETE trial is outlined in CS Table 9, with further details provided in CS Appendix J Table 3. Table 4 in CS Appendix J shows that 43% of the participants were receiving methotrexate at baseline. Participants could continue methotrexate during the RCT if they met certain criteria (see Appendix J Table 1).

The specific patient population included in the trial was patients diagnosed with adult-onset, active psoriatic arthritis (based on the Classification Criteria for Psoriatic Arthritis; CASPAR), who had had a disease duration of ≥6 months. Participants had a tender joint count of ≥3 and a swollen joint count of ≥3, were negative for anti-cyclic citrullinated peptide (anti-CCP) antibodies and rheumatoid factor, and had one active psoriatic lesion and/or a medical history of psoriasis (CS Table 7). The EAG's clinical expert stated that the BE COMPLETE patient population is reflective of how psoriatic arthritis is defined in clinical practice in England in terms of joint considerations, but that skin is not assessed in most rheumatology clinics. Some psoriatic arthritis patients do not have skin involvement when they are changing therapy, skin involvement does not reflect joint involvement and that the CASPAR checklist is not used for diagnosis of active disease in psoriatic arthritis in practice. Our clinical expert also stated that psoriatic arthritis can be diagnosed if the patient does not fulfil the CASPAR criteria and early disease may not fulfil these criteria. The EAG suggests, therefore, that the BE COMPLETE trial population may not fully reflect all patients with active psoriatic arthritis seen in clinical practice.

The participants included in the BE COMPLETE trial had experienced intolerance or an inadequate response (defined as a lack of efficacy after ≥3 months of treatment using an approved dose) to one or two TNFi treatments that had been used for either psoriatic arthritis or psoriasis (CS Table 7). Thus, the trial population includes the biologic-experienced population specified in the company's decision problem (CS Table 1, and as set out for the positioning of bimekizumab in the clinical pathway in CS Figure 1). However, we note that the biologic-experienced population is limited to those who have had an inadequate response to TNFis rather than any other NICE-approved bDMARDs available in the clinical pathway and it is unclear if participants had previously received two cDMARDs earlier in their treatment pathway. In the EAG's clinical expert's view, the patient population is clinically similar to those defined in the company's decision problem.

The BE COMPLETE RCT primary endpoint was ACR50 response (a disease activity measure) at Week 16 (CS section B.3.3.1.3.1). Secondary outcomes included the proportion of PsARC responders at Week 16 (CS Table 10).

4.3.2 BE OPTIMAL

The methodology and statistical analysis of the BE OPTIMAL RCT is described in CS sections B.3.2.1, B.3.3.1.1.2, B.3.3.1.2, B.3.3.1.3, B.3.4.1.1 and Appendix J, and the participant flow through the trial is shown in CS Appendix D.2 Figure 4. CS section B.3.4 provides information on the statistical analysis of the RCT. BE OPTIMAL was a phase 3 trial comparing bimekizumab 160 mg Q4W against placebo Q2W, both administered by SC injection, in the treatment of active psoriatic arthritis (CS Table 7 and CS section B.3.3.1). The trial used the expected licensed dose of bimekizumab (CS Appendix C). The trial also included a reference arm in which adalimumab 40 mg Q2W was administered via subcutaneous injection (CS Table 7) (reasons for including this reference arm are explained in CS section B.3.3.1.1.2). Treatment was delivered over a 52-week period. Participants were randomised to either receive bimekizumab, placebo or adalimumab during the first 16 weeks of treatment (total randomised n = 852). After this, participants entered an active treatment phase, where those who had been randomised originally to active treatments continued these, while those originally randomised to placebo were re-randomised to bimekizumab. The participants who completed the active treatment phase had the option to enter the BE VITAL OLE study. For those not entering the OLE study, there was a 20-week safety follow-up period. Permitted concomitant medication is outlined in CS Table 9, with full details provided in CS Appendix J Table 3. As with the BE COMPLETE trial, participants in BE OPTIMAL could continue receiving methotrexate during the RCT if they met certain criteria (see Appendix J Table 1). Table 4 in CS Appendix J shows that 58% of the participants were receiving methotrexate at baseline in BE OPTIMAL. Rescue medication was permitted in BE OPTIMAL (rescue medication is described in CS Appendix J.1.4). The EAG's clinical expert commented that the rescue medication used mostly reflects what might be used in clinical practice in England, but that apremilast is not used in most NHS trusts.

The BE OPTIMAL trial included participants with active psoriatic arthritis who were bDMARD-naïve (CS section B.3.3.1.1.2). As for the BE COMPLETE trial, to be included in the RCT participants had to have (CS Table 9):

- adult-onset, active psoriatic arthritis (based on the Classification Criteria for Psoriatic Arthritis; CASPAR)
- a disease duration of ≥6 months
- a tender joint count of ≥3 and a swollen joint count of ≥3

- one active psoriatic lesion and/or a medical history of psoriasis and be negative for rheumatoid factor and anti-CCP antibodies.

Participants additionally needed to be suitable for adalimumab treatment. Participants had to be treatment-naïve to any biologics used to manage either psoriatic arthritis or psoriasis (CS Table 9 and CS Appendix J.1.5 Table 3). The population included in this trial does not exactly match either of the populations specified to be of interest in the company's decision problem or where the company is proposing to position bimekizumab in the treatment pathway (that is, in either a) people who have had two cDMARDs and at least one bDMARD or b) in whom TNFis are contraindicated but would otherwise be considered; CS Table 1 and Figure 1). As stated above regarding the BE COMPLETE trial, we suggest that the BE OPTIMAL trial population may not fully reflect all patients with active psoriatic arthritis seen in clinical practice, as clinical expert advice to us is that not all patients in practice will have skin involvement nor necessarily fulfil the CASPAR criteria.

The primary endpoint in the BE OPTIMAL trial was ACR50 response at Week 16 (CS section B.3.3.1.3.1). Secondary outcomes included the proportion of PsARC responders at each visit to Week 52 (CS Table 10).

4.3.3 BE VITAL

The characteristics of the BE VITAL OLE study, which participants from the BE COMPLETE and BE OPTIMAL trials could enter, are not described in detail in the CS. The results for those who entered from BE COMPLETE are presented in CS section B.3.6.1.1.4. The protocol for the study was provided with the CS.[30] Participants are continuing to receive open-label bimekizumab and will be followed up for a period of up to 212 weeks (including the safety follow-up period to 20 weeks after the final dose), which equates to approximately 4 years. Participants who entered BE VITAL from BE COMPLETE are being followed up from Week 16 and those from BE OPTIMAL from Week 52. The week 52 results for the BE COMPLETE participants who entered BE VITAL presented in the CS are from entry into BE COMPLETE rather than from entry into BE VITAL. The bimekizumab dose used was the same as administered in the BE OPTIMAL and BE COMPLETE trials (160mg Q4W via SC injection). Of the participants randomised to BE COMPLETE and BE OPTIMAL trials, 94.5% (378/400) and 91.8% (754/821), entered the OLE, respectively (CS Table 15). BE VITAL data were not used in the company's NMA to compare bimekizumab and ixekizumab, as the NMA focused on PsARC response at around Week 16 of treatment, rather than longer-term outcomes.

4.3.4 BE ACTIVE

The methodology of the BE ACTIVE trial is described in CS sections B.3.2.2 and B.3.3.2.1. BE ACTIVE was a dose-ranging RCT, which included the expected licensed bimekizumab dose of 160 mg Q4W administered via SC injection regimen (CS Table 8) (the other doses used are described in CS Table 8). Of the 206 enrolled participants (CS section B.3.3.2.1), 41 received this dosing regimen (CS Figure 4). The comparator was placebo Q4W, administered by two injections. The trial had a double-bind period, which ended at Week 12 (described in CS Figure 4 and CS Table 12). At the Week 12 visit, participants receiving placebo and some of the dosing regimens were re-randomised, as described in CS Table 12, including some of the participants being re-randomised to bimekizumab 160 mg Q4W.

To be included in the trial, as for the BE COMPLETE and BE VITAL trials, participants had to have (CS Table 9):

- adult-onset, active psoriatic arthritis (based on the Classification Criteria for Psoriatic Arthritis; CASPAR)
- a disease duration of ≥6 months
- a tender joint count of ≥3 and a swollen joint count of ≥3
- have one active psoriatic lesion and/or a medical history of psoriasis and be negative for rheumatoid factor and anti-cyclic CCP antibodies.

Participants were either TNFi-naïve or TNFi-experienced and had had an inadequate response, intolerance to or lost access to treatment (CS Table 8). In line with our critique of the BE COMPLETE trial above (section 4.3.1), the biologic-experienced population is limited to those who have had an inadequate response to TNFis rather than any other bDMARDs available in the clinical pathway in England. Furthermore, it is unclear if participants had previously received two cDMARDs (as per the populations of interest in the CS and in whom the company is positioning bimekizumab; CS Table 1 and CS Figure 1). As we commented for the BE COMPLETE and BE OPTIMAL trials, according to clinical advice to us, not all patients in practice will have skin involvement nor necessarily fulfil the CASPAR criteria, so the BE ACTIVE patient population may not fully represent the patients treated in clinical practice.

4.3.5 BE ACTIVE 2

If participants did not meet the withdrawal criteria for BE ACTIVE and did not receive rescue therapy, they could enter the BE ACTIVE 2 OLE, which had a duration of up to three years. Of the 206 BE ACTIVE participants, 184 (89.3%) enrolled in the OLE (CS section B.3.3.2.1 and CS Table 12). In the OLE, participants received bimekizumab 160 mg Q4W administered by SC injection. Outcomes across both the BE ACTIVE and BE ACTIVE 2

trials included PsARC, measured up to Week 152 (CS Table 8). The BE ACTIVE 2 longer-term efficacy data are not used in the NMA.

4.3.6 Definition of the Psoriatic Arthritis Response Criteria (PsARC) used in the bimekizumab trials

As discussed in section 3.4, PsARC was a key clinical effectiveness parameter in the economic model for the ixekizumab (TA537[10]) appraisal and is the outcome we mainly focus on in our critique of the CS. In the bimekizumab clinical trials, the PsARC response was defined as an improvement in at least two of the following four measures: tender joint count (TJC), swollen joint count (SJC), Patient's Global Assessment of Psoriatic Arthritis (PGA-PsA), and Physician's Global Assessment of Psoriatic Arthritis (PhGA-PsA), one of which must be TJC or SJC and with no deterioration in any of the other measures. Improvement in TJC and SJC were defined as a reduction of ≥30%. Improvement in PGA-PsA and PhGA-PsA were defined as an increase of ≥1 point on a 5-point Likert scale (CS Appendix K, Table 1). The same definition of PsARC response was used in the ixekizumab appraisal. Our clinical expert commented that PsARC response is always defined the same way in clinical trials and it is used by NICE to assess treatment response in psoriatic arthritis.

4.3.7 Summary of trial populations in relation to the company decision problem populations

In Table 1 below, we summarise the extent to which the patient populations included in the BE COMPLETE, BE OPTIMAL and BE ACTIVE trials match those in the company's decision problem and where the company is positioning bimekizumab in the treatment pathway. As can be seen, it is unclear whether any of the populations exactly match those in the decision problem.

Table 1 Summary of the BE COMPLETE, BE OPTIMAL and BE ACTIVE trial populations in relation to the company decision problem population

Trial	Company's decision problem population (reflecting proposed positioning in clinical practice)		EAG comments on the extent to which trial populations match the decision problem populations
	Have had 2 cDMARDs and ≥1 bDMARD	TNFi-contraindicated	
BE COMPLETE population [a]	Participants had been treated with either 1 or 2 prior TNFis (used for either PsA or	Does not report that any patients had a contraindication to TNFi treatments.	It is unclear whether any of the BE COMPLETE population fully matches the company's '2 cDMARDs and ≥1

Trial	Company's decision problem population (reflecting proposed positioning in clinical practice)		EAG comments on the extent to which trial populations match the decision problem populations
	Have had 2 cDMARDs and ≥1 bDMARD	TNFi-contraindicated	
	psoriasis) but experienced intolerance or inadequate response. Unclear if had previously received two cDMARDs.		bDMARD' decision problem population. BE complete does not represent the TNFi-contraindicated decision problem population.
BE OPTIMAL population [a]	Patients with current or previous exposure to any biologics for the treatment of PsA or psoriasis were not included in the trial.	Participants were bDMARD-naïve. Does not report that any patients had a contraindication to TNFi treatments. Unclear if had previously received two cDMARDs.	It is unclear whether any of the BE OPTIMAL population fully matches the company's 'TNFi-contraindicated' decision problem population. Because the BE OPTIMAL participants are bDMARD-naïve they would be suitable for adalimumab treatment unless TNFi contraindicated.
BE ACTIVE population [a]	Some participants were TNFi-experienced (one prior TNFi), with inadequate response, intolerance or loss of access to treatment. Unclear if had previously received two cDMARDs.	Some participants did not have prior exposure to a TNF inhibitor but it is not reported whether any of these had a contraindication to TNFi treatments. Unclear if had previously received two cDMARDs.	It is unclear whether any of the BE ACTIVE population fully matches either of the company's decision problem populations.

Source: EAG compiled table, using information sourced from CS Tables 7 and 8.
bDMARD, biological disease-modifying anti-rheumatic drug; cDMARD(s), conventional disease-modifying anti-rheumatic drug(s); PsA, psoriatic arthritis; TNFi(s), tumour necrosis factor alpha inhibitor(s)
[a] Participants in all the trials had to have at least one active psoriatic lesion and/or a medical history of psoriasis; skin involvement was not specified in the company decision problem and clinical expert advice to the EAG is that the patients with active PsA seen in clinical practice do not necessarily have skin involvement.

4.3.8 Critique of the company's risk of bias assessment

The company included risk of bias assessments of most of the studies included in the NMA in CS Appendix D.3, including of the BE COMPLETE, BE OPTIMAL and BE ACTIVE RCTs of bimekizumab. The company used the Cochrane Risk of Bias 2.0 tool,[31] which is an appropriate method of assessment. The BE VITAL and BE ACTIVE 2 OLEs were not quality assessed by the company and as data from the OLEs are not used in the company's NMAs, we have not critically appraised them here. The EAG's critical appraisals of the BE COMPLETE, BE OPTIMAL and BE ACTIVE trials, using the Cochrane Risk of Bias 2.0 tool, are shown in Appendix 1, alongside those of the company. The company assessed all the trials to be at a low risk of bias. Our assessment of BE OPTIMAL agreed with the company's critical appraisal. However, we had some concerns about the risk of bias in the BE COMPLETE and BE ACTIVE RCTs. There were imbalances in baseline characteristics in both trials, but it is unclear whether these might impact on the PsARC response outcome at Weeks 16 and 12, respectively. We additionally judged that there was a lack of clarity regarding whether double-blinding was sufficiently maintained in the BE ACTIVE trial to prevent knowledge of the intervention received impacting on the assessment of the PsARC response at Week 12 outcome. Please see Appendix 1 for more detail about these uncertainties and our reasoning for our judgements.

4.4 Key results from the pivotal studies of bimekizumab

In this section we briefly summarise the clinical effectiveness outcomes from the company's phase 3 RCTs and signpost the reader to the relevant sections of the CS. We also briefly comment on the PsARC results from the company's phase 2b RCT BE ACTIVE.

The EAG has reviewed the company's approach to trial statistics and has no concerns about these.

4.4.1 BE COMPLETE RCT results

BE COMPLETE provides results for the trial population who have had an inadequate response or were intolerant to prior TNFi therapy (TNFi-IR). Results are summarised in CS Table 16 with further details provided within CS section B.3.6.1.

- Bimekizumab was statistically significantly superior to placebo ($p<0.001$) for the primary outcome ACR50 response at week 16 with 43% of the bimekizumab trial arm achieving this outcome in comparison to 7% of the placebo arm (CS section B.3.6.1.1.1, CS Table 17).

- Bimekizumab was statistically significantly superior to placebo (p<0.001) for all four ranked secondary outcomes at week 16 (CS section B.3.6.1.1.2, CS Table 18). The four ranked secondary outcomes are change from baseline in HAQ-DI, PASI90 response, change from baseline in SF36-PCS and minimal disease activity response.
- The results for the non-ranked secondary outcomes and other outcomes were consistently better with bimekizumab than with placebo (CS section B.3.6.1.1.3, Figure 5, CS Tables 19). These outcomes included the ACR20, ACR50 and ACR70 responder rates to week 16, PASI75, PASI90 and PASI100 at Week 16 in patients with psoriasis involving ≥3% BSA at baseline, composite ACR50+PASI100 response in patients with psoriasis involving at least 3% BSA at baseline, PsARC response, very low disease activity (VLDA) response, proportion of patients achieving modified nail psoriasis severity index (mNAPSI) resolution in the subgroup of patients with nail psoriasis at baseline and axial outcomes (for those with axial involvement at baseline). For PsARC response, which is a key parameter in the cost-effectiveness model, 85.4% of participants in the bimekizumab arm achieved a response in comparison to 30.8% of placebo arm participants.

4.4.2 BE OPTIMAL RCT results

BE OPTIMAL provides results for the trial population who are bDMARD naïve. Results are summarised in CS Table 16 with further details provided within CS section B.3.6.1.

- Bimekizumab was statistically significantly superior to placebo (p<0.001) for the primary outcome ACR50 response at week 16 with 44% of the bimekizumab trial arm achieving this outcome in comparison to 10% of the placebo arm (CS section B.3.6.1.2.1, CS Table 21).
- Bimekizumab was statistically significantly superior to placebo (p<0.001) for all eight ranked secondary outcomes at week 16 (CS section B.3.6.1.2.2, CS Table 22). The first five of the eight ranked secondary outcomes are change from baseline in HAQ-DI, PASI90 response, change from baseline in SF36-PCS, minimal disease activity response and van der Heidje modified total Sharp score in patients with elevated high sensitivity-C reactive protein or ≥1 bone erosion at baseline. The next two outcomes were reported for pooled BE COMPLETE and BE OPTIMAL data: enthesitis-free state in patients with enthesitis at baseline and dactylitis-free state in patients with dactylitis at baseline and the final ranked

secondary outcome was the van der Heidje modified total Sharp score (all patients).

- The results for the non-ranked secondary outcomes and additional efficacy outcomes during the 16-week double-blind RCT period were consistently better with bimekizumab than with placebo (CS sections B.3.6.1.2.3.1, CS Figures 6-9, CS section B.3.6.1.2.3.2, CS section B.3.6.1.2.3.3 and CS Figure 10). These outcomes included disease activity outcomes (ACR20, ACR50 and ACR70 responder rates to week 16, PASI75, PASI90 and PASI100 in patients with psoriasis involving ≥3% BSA at baseline to week 16, composite ACR50+PASI100 response in patients with psoriasis involving at least 3% BSA at baseline, PsARC response, the MDA and VLDA, the proportion of patients achieving mNAPSI resolution in the subgroup of patients with nail psoriasis at baseline), axial outcomes in patients with axial involvement at baseline, HRQoL/functional outcomes and disease progression. For the PsARC response, which is a key parameter in the cost-effectiveness model, 80.3% of participants in the bimekizumab arm achieved a response at week 16 in comparison to 40.2% of placebo arm participants.
- Patients in the bimekizumab arm during the double-blind treatment period sustained their treatment responses from the end of the 16-week treatment period to week 52. Patients who switched from placebo to bimekizumab at the end of the 16-week double-blind period attained levels of response during the active-treatment blind period that broadly matched those of the participants in the original bimekizumab arm (CS sections B.3.6.1.2.3.1, CS Figures 6-9, CS section B.3.6.1.2.3.2, CS section B.3.6.1.2.3.3 and CS Figure 10).
- The proportion of patients with no radiographic progression was higher in the bimekizumab arm (84.8%) than in the placebo arm (82.5%) at week 16 (CS B.3.6.1.2.3.4).

4.4.3 Supporting clinical effectiveness evidence

The company present supporting evidence from their phase 2b RCT BE ACTIVE and it's open-label extension, BE ACTIVE 2 in CS section B.3.6.2 and CS Appendix L. PsARC response outcome data from BE ACTIVE is included in the company's NMA with the subgroup of TNFi-experienced participants contributing data to the TNFi-experienced NMA and the subgroup of TNFi-naïve participants contributing data to the TNFi-CI NMA. In the full analysis set, proportionally more participants experienced a PsARC response at Week

12 in the bimekizumab 160 mg Q4W arm than the placebo arm (88% and 48%, respectively) (CS Appendix L Table 25).

4.4.4 Long-term data from the pivotal bimekizumab studies

4.4.4.1 BE COMPLETE

The double-blind treatment period of BE COMPLETE ended after 16 weeks of treatment. Participants were then able to enter the open-label extension study BE VITAL in which all patients received bimekizumab. Results for those who entered from BE COMPLETE are presented in CS section B.3.6.1.1.4. For the outcomes where we could directly compare the 16-week results to the 52-week results [ACR50 response, PASI90 response, PsARC, MDA response, change from baseline in HAQ-DI and Short Form-36 Physical Component Summary (SF-36 PCS)] patients originally randomised to the bimekizumab arm had maintained or improved outcomes except for the PsARC response which was attained by 85.4% of participants at week 16 but had fallen slightly to 80.1% at week 52 Participants originally randomised to placebo who crossed over to bimekizumab at the end of the 16-week double blind period, experienced more improvement in all measured outcomes at week 52 than was experienced at week 16.

4.4.4.2 BE OPTIMAL

Participants in the BE OPTIMAL RCT crossed over to bimekizumab after the initial 16-week double-blind treatment period. The long-term (52 week) results are presented in CS Section B.3.6.1.2.3. CS Figures 6 to 8 show that participants who received bimekizumab in the 16-week double blind period slightly improved their responses (ACR 20/50/70, PASI 75/90/100, composite ACR50+PASI100) from week 16 until week 52, while their PsARC response was largely maintained (80.3% classed as responders at week 16 versus 79.1% at week 52). The response of participants who switched from placebo to receive bimekizumab between weeks 16 and 52 improved such that by week 52 there was little difference between those initially randomised to placebo and those who received bimekizumab throughout the RCT. A similar pattern of response was observed for the MDA and VLDA outcomes (CS Figure 9), the axial outcome (for patients with axial involvement at baseline) (CS section B.3.6.1.2.3.2) and HRQoL outcomes (CS Figure 10).

4.4.4.3 BE ACTIVE 2

Supporting long term evidence from the open-label BE ACTIVE 2 study which followed on from the 12-week phase 2 BE ACTIVE RCT is presented in CS Figure 11 (ACR 20/50/70, PASI 75/90/100), Figure 12 (MDA, VLDA, resolution of dactylitis, resolution of enthesitis) and Table 24 (composite ACR50+PASI100, HAQ-DI, SF-36 PCS, PsARC). These data also

show that responses were maintained from the end of the double-blind period to the end of the open-label extension (week 156).

4.5 Critique of the company's indirect treatment comparison/ network meta-analyses

The bimekizumab trials were placebo controlled, and there is no direct evidence comparing bimekizumab with the company's selected comparator ixekizumab. Therefore, an indirect comparison is used to assess the similarity of clinical effect between bimekizumab and ixekizumab. An indirect comparison, in the form of a network meta-analysis (NMA) has been undertaken for two sub-populations and a mixed population:

- TNFi-experienced patients to represent the company's decision problem population of patients who have had "*two conventional DMARDs (cDMARD) and at least one biological-DMARD (bDMARD*)". The extent to which this NMA sub-population matches the company's decision problem population is uncertain because the trials in this network included patients who had received different numbers of prior DMARDs. The EAG notes that NMAs for a sub-population of TNFi-experienced patients has been a common feature of previous NICE technology appraisals in this disease area, so this is following an existing precedent. This group includes, but is broader than, the population in the key bimekizumab RCT BE COMPLETE who had an inadequate response to or an intolerance to prior TNFi therapy.
- TNFi-CI patients (i.e. patients for whom TNFi is contraindicated) to represent the company's decision problem population of patients for whom "*Tumour necrosis factor inhibitors (TNFi) are contraindicated but would otherwise be considered*". As defined at the end of CS section B.1.1, this network uses studies from a b/tsDMARD-naïve network, but with TNFi treatments removed.
- Mixed population (i.e. patients who are b/tsDMARD-naïve or TNFi-experienced) for safety outcomes. Section B.3.9.1 of the CS explains RCTs were pooled because the safety profiles of the interventions included in the NMA were not expected to differ between treatment-naïve or treatment-experienced populations.

The NMA presented in the CS reports on more comparators than were required for this appraisal because it was conducted from a global perspective. It is therefore termed the "*global NMA*". The SLR (critiqued in 4.1 of this report) identified 66 unique trials and the company included 41 of these in the global NMA (of which three include bimekizumab and three ixekizumab, CS Appendix D Table 25). All RCTs in the TNFi-experienced and TNFI-CI

populations were placebo controlled, hence the inclusion of additional comparators is not expected to impact the indirect comparison between bimekizumab and ixekizumab. The mixed population added a comparison between ixekizumab and adalimumab (SPIRIT-H2H) which created a series of loops between bimekizumab, ixekizumab, adalimumab, upadacitinib, and placebo. Besides these, the inclusion of additional comparators from the global NMA is expected to have no impact on the indirect comparison between bimekizumab and ixekizumab. The 25 studies identified but excluded from the global NMA are listed in CS Appendix D Table 24 (none of these studies involved bimekizumab or ixekizumab as a treatment). The CS states (CS section B.2.1.2) that all the previously considered key clinical efficacy outcomes are included in the NMA for the current submission and thus the CS reports NMAs for eight efficacy and HRQoL outcomes and three safety outcomes (with other outcomes presented in CS Appendix D and the NMA reports that informed the CS[32; 33]) but the EAG notes that only the PsARC and treatment discontinuation NMA outcomes inform the cost-comparison model:

- Efficacy and HRQoL outcomes (separately for TNFi-experienced and TNFi-CI patients using week 16 data where available)
  - ACR20, ACR50, ACR70
  - PASI75, PASI90, PASI100
  - PsARC
  - MDA
  - HADQ-DI
  - Enthesitis resolution
  - Dactylitis resolution
  - Pain VAS
- Safety outcomes (mixed population as the safety profiles were not expected to differ by prior b/tsDMARD exposure)
  - Serious adverse events
  - Discontinuation
  - Discontinuation due to adverse events

In our critique we focus on the trials for bimekizumab and the company's chosen comparator of interest (ixekizumab) which are listed in CS Table 25 and the outcomes that were important drivers of cost-effectiveness in the appraisal of ixekizumab (TA537[10]). These outcomes were the **PsARC response rate** which was used to determine treatment response in the base-case analysis and the **annual treatment discontinuation rate**. The EAG's

validation and scenarios used the trials which created indirect evidence between bimekizumab and ixekizumab but omitted all the other irrelevant comparators in the company's global NMA. Other clinical effectiveness parameters that contributed data to the cost-effectiveness model used for the TA537 ixekizumab appraisal were the PASI score and the HAQ-DI score which were both used to determine resource use, costs and health state utility values. The company has summarised the clinical efficacy outcomes and manufacturer approaches/assumptions appraised in existing published NICE guidance for the treatment of psoriatic arthritis in CS Table 3.

4.5.1 Identification and selection of studies included in the network meta-analyses

The company conducted one SLR, which was used both to identify clinical trials of bimekizumab but also of other treatments for psoriatic arthritis. We have critiqued the company's SLR methods in section 4.1 of this report and believe it is unlikely that any studies have been missed.

The inclusion criteria for the global NMA are reported in CS appendix D.1.9. Only treatments relevant to clinical practice and used in approved dosing regimens (i.e. recommended by current clinical guidelines, licensed by key regulatory bodies and/or routinely used) or at a late state of development (with doses evaluated in clinical trials) and hence a potential future competitor for bimekizumab were eligible for inclusion. Placebo was the common comparator.

The CS presents example network diagrams for the ACR50 outcome in the TNFi-experienced population and the TNFi-CI population (CS Figure 13). Here we present example network diagrams for the PsARC response rate in Figure 2 [because this outcome was used as the measure of treatment response in previous NICE appraisals, including that of ixekizumab (TA537), and this parameter was an important driver of cost-effectiveness in the appraisal of ixekizumab (TA537)] and treatment discontinuations in Figure 3 which includes further indirect evidence between bimekizumab and ixekizumab via adalimumab and upadacitinib.

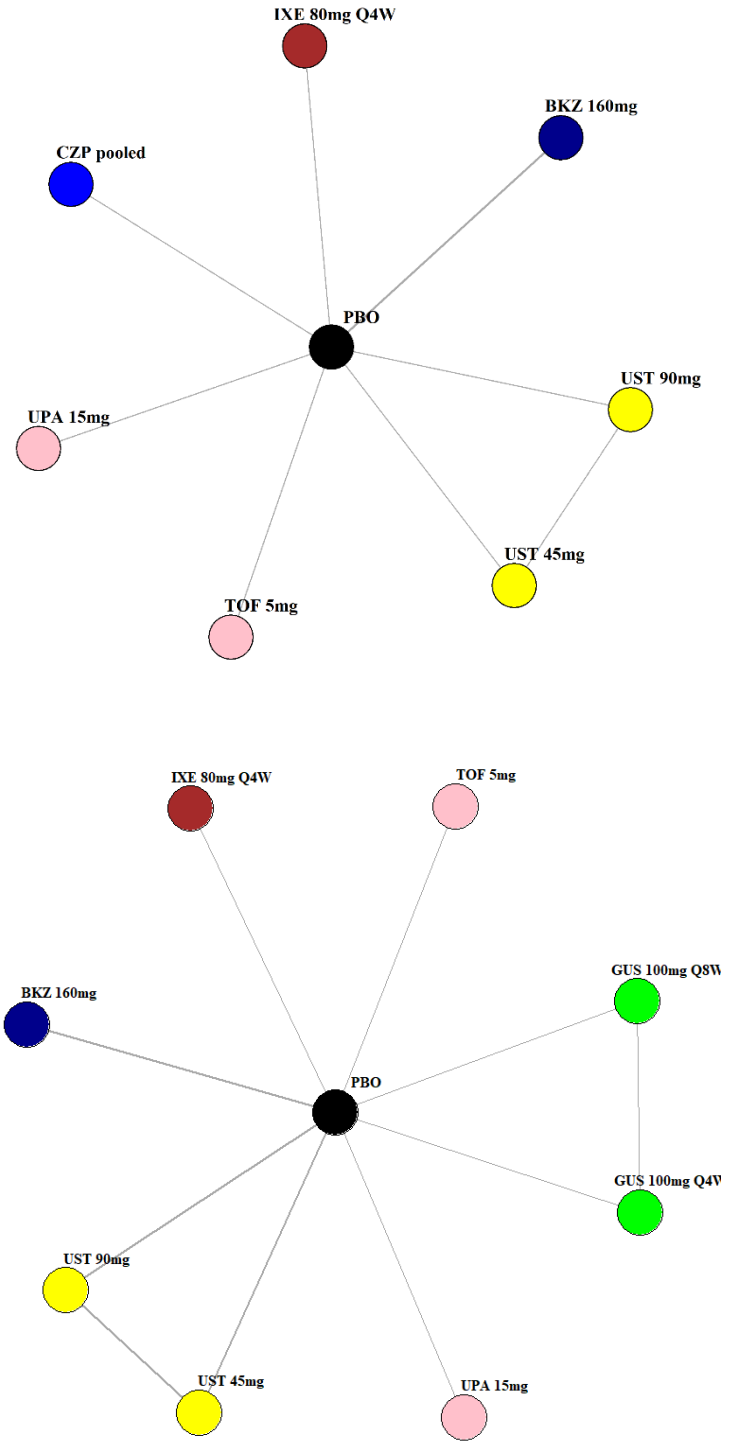

Figure 2 Network of evidence for the PsARC outcome in the TNFi-experienced population (top) and the TNF-CI population (bottom)

Source: Reproduced from CS Appendix D Figure 9 and CS Appendix D Figure 21
BKZ, bimekizumab; CI, contra-indicated; CZP, certolizumab pegol; GUS, guselkumab; IXE, ixekizumab; PBO, placebo; QXW, every X weeks; TNFi, tumour necrosis factor alpha-inhibitor; TOF, tofacitinib; UST, ustekinumab; UPA, upadacitinib

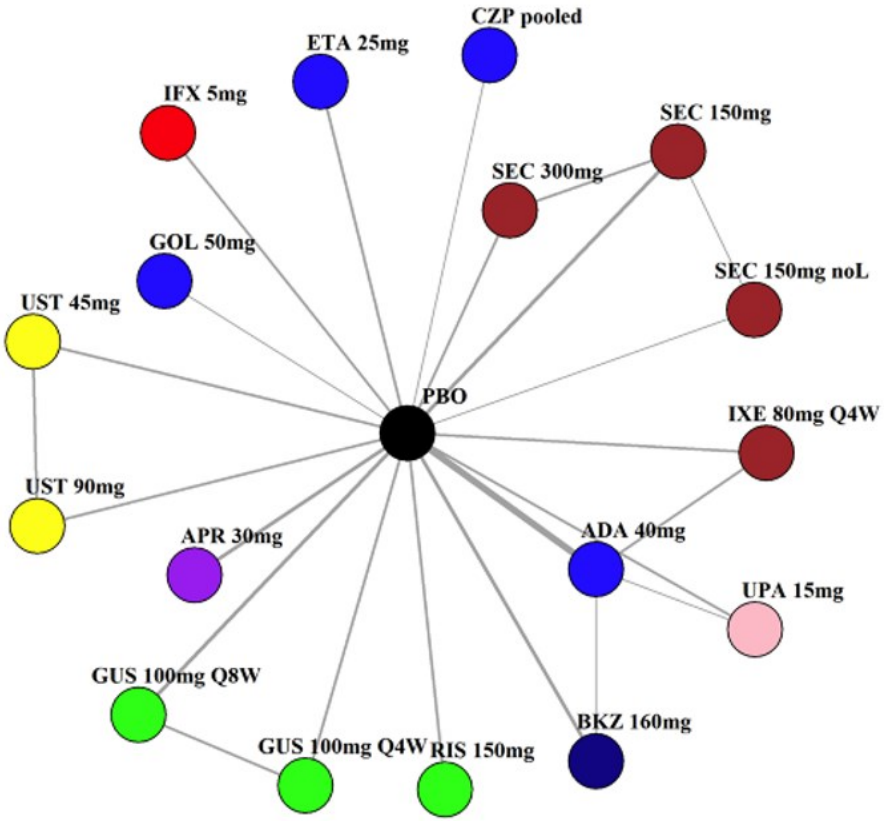

Figure 3 Network of evidence for the Discontinuation outcome in the mixed population (patients who are b/tsDMARD-naïve or TNFi-experienced)

Source: Reproduced from CS Appendix D Figure 23
ADA, adalimumab; APR, apremilast; BKZ, bimekizumab; CZP, certolizumab pegol; ETA, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; noL, no loading; QXW, every X weeks; RIS, risankizumab; SEC, secukinumab; TNFi, tumour necrosis factor alpha-inhibitor; UST, ustekinumab; UPA, upadacitinib

4.5.2 Characteristics of studies included in the indirect treatment comparison/ network meta-analyses

Details about the studies included in the global NMA network are primarily reported in CS Appendix D. Here we focus on providing details on RCTs for the company's chosen comparator ixekizumab and comparing these with the bimekizumab RCTs. The bimekizumab and ixekizumab RCTs included in the NMAs are shown below in Table 2 together with the other studies which form indirect links between bimekizumab and ixekizumab. Note that BE ACTIVE included TNFi-experienced and TNFi-naïve participants and that subgroup data was available which enabled BE ACTIVE participants to be included in either the TNFi-experienced or TNFi-CI network as appropriate.

Table 2 List of RCTs included in the EAG validation and scenario NMAs

RCT name[a]	Intervention	TNFi-experienced NMA inclusion	TNFi-CI NMA inclusion	Mixed population (b/tsDMARD-naïve or TNFi-experienced)
BE ACTIVE	PBO/BKZ	Yes	Yes	Yes
BE COMPLETE	PBO/BKZ	Yes	No	Yes
BE OPTIMAL	PBO/BKZ/ADA	No	Yes	Yes
SPIRIT-P1	PBO/IXE/ADA	No	Yes	Yes
SPIRIT-P2	PBO/IXE	Yes	No	Yes
SPIRIT-H2H	IXE/ADA	No	No	Yes
ADEPT	PBO/ADA	No	No	Yes
M02-570	PBO/ADA	No	No	Yes
Select-PSA-1	PBO/UPA/ADA	No	No	Yes
Select-PSA-2	PBO/UPA	No	No	Yes

Source: Reproduction of CS Table 25 with additional trials and a column for the mixed population added by the EAG.
ADA, adalimumab; BKZ, bimekizumab; IXE, ixekizumab; NMA, network meta-analysis; PBO, placebo; TNFi, tumour necrosis factor alpha inhibitor; TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated; UPA, upadacitinib
[a] The company used a wider selection of trials and comparators for the global NMA

For simplicity, and to avoid adding additional heterogeneity to the network, the EAG's validation and scenarios only include those studies listed in Table 2, i.e. those which formed an indirect link between bimekizumab and ixekizumab. In the TNFi-experienced and TNFi-CI populations this included the common comparator placebo (Limited network), whilst in the mixed population, this added further common comparators adalimumab and upadacitinib (extended network).

4.5.2.1 Methodological characteristics

CS Appendix D Table 25 lists the basic features of the 41 studies included in the global NMA with the bimekizumab and ixekizumab RCTs shown in bold type. Note that one of the listed ixekizumab RCTs, SPIRIT-H2H, was not included in either the TNFi-experienced or TNFi-CI NMA networks (it was included the b/tsDMARD-naïve NMA network which is not relevant to the company's decision problem population, and the mixed population safety NMA networks).

Key efficacy outcomes used in the NMAs, including PsARC which informs the model, were assumed to be for a 12-week timepoint in the BE ACTIVE RCT (we were unable to find BE ACTIVE PsARC data in the published paper[21] or the CSR[34]) and a 16-week timepoint in the BE COMPLETE and BE OPTIMAL bimekizumab RCTs whereas in the ixekizumab RCTs SPIRIT-1 and SPIRIT-2 the PsARC outcome was from the 24-week timepoint, although data are also available from a 12-week timepoint. The EAG conducted scenarios using the 12-week ixekizumab data for PsARC which showed the 24-week analysis to be a conservative analysis.

4.5.2.2 Patients' baseline characteristics

CS Appendix D Tables 38, 39, and 40 provide a summary of the baseline patient characteristics, disease characteristics and prior or concomitant therapies across the 41 studies included in the global NMA. For the trials included in the EAGs validation and scenario NMAs (Table 2) the age of participants was similar, the proportion of male participants ranged from 34% to 59% and the majority of participants were White. CS Appendix D.1.11 describes the heterogeneity identified across patient baseline and disease characteristics and across prior or concomitant therapy use.

We have compared the bimekizumab and ixekizumab RCTs participants in the placebo controlled trials in terms of their treatment experience with TNF inhibitors (Appendix 2). The bimekizumab and ixekizumab RCT participants included in the TNFi-experienced NMA network had all been exposed to at least one prior TNF inhibitor treatment and some of those from BE COMPLETE and SPIRIT-P2 could have received two prior TNF inhibitors. Only the SPIRIT-2 RCT specifically stated that participants had previously been treated with one or more cDMARDs. The bimekizumab and ixekizumab RCT participants included in the TNFi-CI network had no prior exposure to TNF inhibitors and none of the trials described the participants as having a contraindication to TNF inhibitors. However, although the bimekizumab and ixekizumab RCT participants in the TNFi-CI network do not have a contraindication to TNF inhibitors, the EAG notes that NICE have already recommended ixekizumab for patients when TNF-alpha inhibitors are contraindicated but would otherwise be considered (TA537) based on evidence from the SPIRIT-P1 trial.

Overall, although there are some differences between the bimekizumab and ixekizumab RCT participants in terms of their treatment experience with TNF inhibitors, these differences are of a similar nature to those noted in previous NICE appraisals in this topic area. Consequently, we believe that the bimekizumab and ixekizumab RCT trial populations included in the company's TNFi-experienced and TNFi-CI NMA networks provide evidence

that is suitable for decision making in terms of the two population groups defined in the company's decision problem.

4.5.2.3 Risk of bias assessments

The company made a risk of bias assessment using the Cochrane Risk of Bias 2.0 tool[31] for 63 of the 66 studies identified in the SLR (as these had full text publications), including the 41 studies that contributed to the global NMA. The risk of bias assessments are reported in CS Appendix D Table 41. It was not feasible for us to independently assess all 41 studies that were included in the global NMA but we have conducted our own assessment of the bimekizumab RCTs (see section 4.3.8 and Appendix 1 of this report) and cross-checked the company's assessment of the ixekizumab RCTs against the risk of bias assessments conducted by the EAG for the ixekizumab appraisal TA537. We agree that BE OPTIMAL is at a low risk of bias, but we had some concerns about the risk of bias for the BE COMPLETE and BE ACTIVE RCTs (for full details please refer to section 4.3.8 and Appendix 1 of this report). We agree that the ixekizumab trials are at a low overall risk of bias.

4.5.3 Clinical heterogeneity assessment

When asked about the meta-regression approach to adjust for heterogeneity in time since diagnosis and concomitant use of methotrexate described in CS Appendix D.1.11.2 (clarification question A3) the company responded that "*none of the highly heterogeneous baseline characteristics were identified as confounders of treatment effect*" and that "*The heterogeneity primarily centred around prognostic variables, leading to the assumption that the variation primarily influenced the baseline risk within the population, rather than impacting the treatment effect directly*" despite their reporting time since diagnosis and concomitant use of methotrexate as potential treatment effects modifiers. Because of this, the individual baseline characteristics and their impact on treatment effect were not modelled separately but instead modelling addressed differences in baseline risk across the patient population following a similar methodology to that proposed in Technical Support Document 3 guidelines[35] and employed in TA711 for gulselkumab. The clarification response A4 Tables 1 to 4 show the variations in baseline risk across the different NMA networks.

The EAG agrees this was the correct approach as we would expect heterogeneity in placebo response, attributable to heterogeneity in measured and unmeasured patient-level covariates or placebo creep, to be a treatment effect modifier.

There were some differences in baseline potential treatment effect modifiers (e.g. PASI total score, proportion receiving concomitant methotrexate and proportion receiving concomitant DMARDs) across bimekizumab and ixekizumab studies. There was a lack of reporting of

other potential effect modifiers (e.g. prior bDMARDs, cDMARDs). The observed differences combined with the lack of reporting for some potential effect modifiers suggests to the EAG that a random effects NMA would normally be preferred. However, there are insufficient datapoints to reliably calculate random effects in the EAG's limited network (bimekizumab-ixekizumab) and including all trials the global network would, in our view, introduce further heterogeneity. The EAG's use of the extended network for discontinuation, which includes all indirect evidence between bimekizumab and ixekizumab, added further heterogeneity with the Select-PSA studies of upadacitinib having the highest mean PASI scores.

Outcomes were reported at different timepoints with the company using timepoints closest to 16 weeks (the timepoint of the primary outcomes in the bimekizumab trials). Some study designs incorporated cross-over (BE OPTIMAL), early escape (SPIRIT-P1, SPIRIT-P2), and rerandomisation (BE ACTIVE, BE COMPLETE). The company concede these differences may introduce bias, but that this was mitigated by use of pre-crossover data (CS section B.3.9.6). The EAG mostly agrees with this. However, SPIRIT-P1 and P2 randomised inadequate responders on placebo to one of the two ixekizumab doses at week 16 whilst the company used 24-week data for the analysis. Nevertheless, we found use of the 24-week data to be conservative compared to the 12-week data. Furthermore, whilst BE ACTIVE rerandomised placebo patients at week 12 to one of the bimekizumab doses we assume week 12 data were used in the analysis (because no patients received placebo after week 12), but this was not explicitly stated in the CS.

There were also differences in baseline (placebo) response rate between studies which may have been a function of heterogeneity across trial populations or placebo creep due to earlier diagnosis, changes in routine clinical management, or patient expectations of benefit. The company correctly explored models adjusting for this in the analysis.

4.5.4 Critique of the indirect treatment comparison/ network meta-analysis modelling approach

4.5.4.1 Data inputs to the indirect treatment comparison/ network meta-analyses

Data used in the NMA for PsARC and discontinuations are reported in CS Appendix D Table 31 (PsARC, TNFi-experienced population), CS Appendix D Table 36 (PsARC, TNFi-CI population), and CS appendix D Table 37 (discontinuations, mixed population). As noted at the start of section 4.5 in this report, the company used a "global network" to conduct the NMA which included many non-relevant comparators for this appraisal. Inclusion of this wider set of studies would not be expected to impact the PsARC analysis (and our validation

confirms this), as all studies for TNFi-experienced and TNFi-CI populations are placebo-controlled with no indirect evidence comparing bimekizumab and ixekizumab. However, use of a global network in the adjusted (baseline risk) analysis may have introduced bias if placebo response is likely to have changed over time.

As noted above, the discontinuations NMA is conducted in a mixed population which introduces additional connection between bimekizumab and ixekizumab via adalimumab and upadacitinib. Inclusion of additional comparators from the global network would again not be expected to impact results. A continuity correction is reasonably applied to BE ACTIVE and the University of Washington study where zero events were observed for discontinuations.

Baseline risk (placebo response) was included as a covariate to reduce heterogeneity in patient populations. There are notable differences in baseline risk between studies as reported in Tables 1, 3, and 4 of the company's clarification response A4.

4.5.4.2 Statistical methods for the NMA

The NMAs were well conducted and follow guidance within NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 2 and 3.[35; 36] The company explored fixed and random effects models and adjusted for baseline risk (placebo response). The EAG validated model results for the best fit model for the PsARC and discontinuations endpoints. We used our own code as we were unable to run the Just Another Gibbs Sampler (JAGS) code provided in response to clarification question A1 as no annotation of the data names was provided. Nevertheless, there were no obvious errors. Despite the presence of direct and indirect evidence between bimekizumab and ixekizumab in the mixed population network, no inconsistency checking appears to have been undertaken.

Whilst the company NMAs were conducted using the global network, the EAG ran scenarios using the limited and extended networks for PsARC and discontinuations, respectively. For the adjusted models we used the methodology developed by Achana & colleagues.[37]

4.5.4.3 Choice between NMA models

Best model fit between adjusted (for baseline risk) or unadjusted models was determined by whether or not the coefficient on baseline risk was statistically significant which the EAG deems a reasonable approach. Choice between fixed and random effects was dependent upon the deviance information criterion (DIC); if random effects were at least three lower than the fixed effects then random effects was chosen. Results were only reported for the best fit model.

The unadjusted fixed effects model was preferred for PsARC across both TNFi-experienced and TNFi-CI populations. Other models were a similar fit, and none of the coefficients on baseline risk were statistically significant or meaningful (document B, Table 26). The EAG validated the company calculation for the best fit models using the limited network and obtained similar results to the company's global NMA.

For discontinuations in the mixed population, an adjusted fixed effect model was preferred, DIC was lowest and the coefficient on baseline risk was statistically significant (document B, Table 26). However, in one of the company's accompanying NMA reports (Section 5.3.3, Table 115), an unadjusted random effect model was preferred. We are aware that there is an updated NMA report, which unfortunately we did not receive, which is where the preferred adjusted fixed effect model is reported. Without sight of the updated NMA report on discontinuations we cannot explain this inconsistency, particularly as the same underlying data appears to have been used for both analyses (NMA report section 12.10; CS D1.10.13, Table 37). The EAG found similar results for the adjusted fixed effect model using the global network, and when using the extended network albeit the effect of baseline risk was no longer statistically significant.

4.5.5 Summary of the EAG's critique of the company's network meta-analyses

- The company's NMA approach was appropriately conducted, including model selection rules.
- Endpoint timing selection minimised bias in terms of study design in terms of crossover / rerandomisation / early escape.
- Heterogeneity between studies may have been exacerbated by use of global network but random effects was not always plausible given the number of datapoints to studies. However, we found use of the global network did not bias results.
- The model for discontinuations showed a statistically significant interaction with baseline risk only for the global network which may be a function of change in standard care over time.

4.6 Results from the NMAs

The company present the results for univariate NMAs comparing bimekizumab 160mg Q4W versus ixekizumab 80 mg Q4W in CS sections B.3.9.4.2 (TNFi-experienced population), B.3.9.4.2 (TNFi-CI population) and B.3.9.4.4 (SAEs, discontinuation and discontinuation due to AEs in mixed population of b/tsDMARD-naïve and TNFi-experienced patients). The company does not present results for the multivariate NMAs in CS Document B or CS Appendix D (these were not conducted for every outcome but could be found in the NMA

report included in the reference pack for the ACR and PASI outcomes with results being similar to the results of the univariate analyses). The model fit statistics (such as the deviance information criterion) are summarised in CS Table 26 for four models (fixed-effect, unadjusted model; random-effects, unadjusted model, fixed-effects, baseline risk-adjusted model and random-effects, baseline risk-adjusted model), with the preferred model in bold text. The results from the preferred models against all UK licenced comparators are provided in CS Appendix D.4 and this also includes full details of the model fit statistics for each network. The CS does not present the results for alternative models, only the results from the company's preferred models for each outcome. There were closed loops only for the mixed population (discontinuations) but checks for consistency are not reported.

4.6.1 Efficacy outcomes

As shown in CS Figures 14 and 15, for the NMA comparison of bimekizumab 160mg versus ixekizumab 80 mg Q4W there was a statistically significant difference in favour of bimekizumab for the ACR20, PASI100, PsARC and enthesitis outcomes in the TNFi-experienced population and a statistically significant difference in favour of bimekizumab for the ACR70 and PsARC outcomes in the TNF-CI population. Here, we focus on the PsARC response rate because this outcome was an important driver of cost-effectiveness in the appraisal of ixekizumab (TA537) (Table 3). For the remaining outcomes shown in CS Figures 14 and 15 there were no statistically significant differences between bimekizumab and ixekizumab (i.e. ixekizumab was not statistically significantly better than bimekizumab for any of the outcomes shown in CS Figures 14 or 15).

Table 3 PsARC outcome from the company NMAs for the comparison of bimekizumab 160mg versus ixekizumab 80 mg Q4W

Population	OR (95% CrI)	Company preferred model
TNFi-experienced	2.82 (1.30, 6.02)[a]	Fixed effect, unadjusted
TNFi-CI	2.05 (1.06, 3.91)[a]	Fixed effect, unadjusted

Source: Data extracted by the EAG from CS Figure 14 and CS Figure 15.
CrI, credible interval; NMA, network meta-analysis; OR, odds ratio; PsARC, Psoriatic Arthritis Response Criteria; Q4W, every 4 weeks; TNFi, tumour necrosis factor alpha inhibitor; TNFi-CI, tumour necrosis factor alpha inhibitor-contra indicated
[a] Statistically significant difference in favour of bimekizumab

4.6.2 HRQoL outcomes

The HAQ-DI outcome could only be assessed by NMA for the TNFi-experienced population and, as CS Figure 14 shows, there was no statistically significant difference between bimekizumab 160mg versus ixekizumab 80 mg Q4W for this outcome.

4.6.3 Safety outcomes

Safety outcomes were assessed using data for a mixed population. But despite pooling a greater number of participants, the company notes in CS section B.3.9.4.4.1 that all of the safety NMAs are based on a small number of events. CS Figure 16 shows the forest plot for SAEs, discontinuation and discontinuations due to AEs in the mixed population and there was no significant difference between bimekizumab and ixekizumab for these outcomes.

4.7 Conclusions on the clinical effectiveness evidence

- The company conducted a comprehensive systematic literature review for RCTs which informed their submission including their NMA. It is unlikely any RCTs have been missed.
- The clinical effectiveness evidence for bimekizumab comes from two placebo-controlled phase 3 RCTs [BE COMPLETE and BE OPTIMAL (which also included an adalimumab reference arm)], an open-label extension BE VITAL which participants from BE COMPLETE and BE OPTIMAL could enter, one placebo-controlled phase 2 RCT BE ACTIVE and its open label extension BE ACTIVE 2.
- The bimekizumab trials were well designed and appear to have been well executed and we agreed with the company that the BE OPTIMAL RCT has a low risk of bias. Our judgement on the overall bias for the BE COMPLETE and BE ACTIVE RCTs is 'Some concerns' in contrast to the company who believe these trials are at a low risk of bias.
- The bimekizumab RCTs provide evidence for the superiority of bimekizumab over placebo over the relatively short duration of the double-blind trial periods (16 weeks for BE COMPLETE and BE OPTIMAL, 12 weeks for BE ACTIVE). Non-comparative longer term data provides evidence that bimekizumab continues to provide clinical benefit beyond the double-blind trial periods (to 52 weeks for BE COMPLETE participants enrolled in BE VITAL, to 52 weeks for BE OPTIMAL and to week 156 for BE ACTIVE 2).
- The participants enrolled in the bimekizumab RCTs appear reasonably generalisable to patients treated within the NHS and they are comparable to the trial populations for ixekizumab, the company's chosen comparator for the cost-comparison. It is unclear whether any of the bimekizumab trial populations exactly matches those defined in the company's decision problem, primarily because it was not clear whether they had previously received two cDMARDs or whether they had a contraindication to TNFi treatments.

- The NMA presented in the CS reports on more comparators than were required for this appraisal because it was conducted from a global perspective. NMAs were undertaken for two sub-populations for efficacy and HRQoL outcomes (TNFi-experienced and TNFi-contraindicated) and a mixed population for safety outcomes (TNFi-experienced or b/tsDMARD-naïve).
- The NMAs were well conducted and follow NICE DSU TSD guidance. Both fixed and random effects models were explored and the company appropriately adjusted for baseline risk (placebo response). There is no evidence that consistency checking was undertaken for the mixed population network which includes both direct and indirect evidence. We have validated the PsARC and discontinuation NMA results.
- The inclusion of a large number of irrelevant comparators in the company's global network exacerbated heterogeneity between studies and although such heterogeneity means the random-effects model would normally be preferred it was not always possible to run a random-effects model because there were insufficient data points. However, we found that the use of the global network did not bias the results.
- Results from the company's NMA showed a statistically significant difference in favour of bimekizumab when compared with ixekizumab for some efficacy outcomes and no statistically significant differences between bimekizumab and ixekizumab for the remaining outcomes in both the TNFi-experienced and TNFi-CI populations. There were no statistically significant differences in safety between bimekizumab and ixekizumab in the mixed population. We consider the company's assertion of similarity in efficacy and safety between bimekizumab and the company's chosen comparator ixekizumab to be acceptable.

5 SUMMARY OF THE EAG'S CRITIQUE OF COST COMPARISON EVIDENCE SUBMITTED

5.1 Decision problem for the cost comparison

5.1.1 Population, intervention and comparator

We discuss the company's specification of the population for the decision problem in section 3.1 above. The model uses the baseline characteristics from the BE OPTIMAL and BE COMPLETE trials (CS Table 31) to estimate mortality for the TNFi-CI and b/tsDMARD experienced populations, respectively. These are broader populations than the target population described in CS section B.1.1, but population demographics only affect mortality rates so there is minimal impact on cost estimates. The bimekizumab trial population demographics are broadly comparable to those from the key trials for ixekizumab (SPIRIT-P1 and SPIRIT-P2; TA537)[10] (discussed above in section 0).

Bimekizumab is supplied as pre-filled pens or pre-filled syringes, which patients can self-administer. The dose for bimekizumab is 160mg (one injection), administered via SC injections every four weeks, without an initial loading dose. The SmPC states bimekizumab can be given alone or in combination with methotrexate for the treatment of active psoriatic arthritis. The EAG observes that the company's model only includes the costs of bimekizumab monotherapy.

The company chose ixekizumab as the comparator for their analysis. Ixekizumab is also available as pre-filled pens or pre-filled syringes and is administered via SC injections, with a loading dose of 160mg (two 80mg injections) at Week 0 then 80mg every four weeks thereafter, and may be given alone or in combination with methotrexate.[38]

As with their approach for bimekizumab, the company's model does not include the cost of methotrexate in the costs for ixekizumab therapy. It is not clear what proportion of patients would be receiving methotrexate combination therapy in UK clinical practice, but the EAG notes that similar proportions of patients in the two ixekizumab RCTs and three bimekizumab RCTs received concomitant methotrexate (please see section 3.3 for more detail). In this case, the costs for methotrexate is likely to be equivalent for the two treatments, so excluding them in the model is acceptable. In addition, the costs of methotrexate for psoriasis are negligible[39] and likely to be similar for psoriatic arthritis.

The CS explains the reasons why ixekizumab is considered the most relevant comparator in the scope, including:

- Similar mechanism of action to bimekizumab
- Accepted as an appropriate comparator in the company's previous cost-comparison submission (Bimekizumab for treating moderate to severe chronic plaque psoriasis; TA723)[3]
- Similar clinical efficacy and safety profile to bimekizumab
- Seven clinical experts at a UK advisory board considered ixekizumab to be the most appropriate comparator

Based on NICE guidance for EAGs on cost comparison appraisals, the EAG believes the company's choice of comparator is appropriate (as discussed in section 3.3).

5.1.2 Company's model structure

The company's model structure is shown in CS Figure 17 and described in CS section B.4.2.1. The model uses a 10-year time horizon. The EAG notes that the model structure and time horizon are consistent with the previous cost-comparison for risankizumab for psoriatic arthritis (TA803).[2] A summary of the model inputs is presented in CS Table 33, which we discuss in section 5.1.3.

The company's base case does not include discounting, as per the guidance for cost-comparison appraisals,[4] but the company explores discounting in scenario analyses. The analyses presented in the CS include the PAS discount for bimekizumab and use the list price for ixekizumab. We present the results of the company's analyses, including the PAS discount for ixekizumab, in a separate confidential appendix to this EAG report.

5.1.2.1 Assumptions

The company make the following assumptions in their base case analysis (also summarised in CS Table 34):

- Based on the company's NMA (CS section B.3.9), bimekizumab and ixekizumab are assumed to be equivalent in terms of clinical efficacy (PsARC response rate), treatment discontinuation rates and adverse events.
- Patients remaining alive during the trial period do not discontinue treatment, and the proportion of patients who do not respond to treatment at 16 weeks is the same for both therapies. Assessing ixekizumab PsARC response at 20 weeks is explored in a scenario analysis.

- Patients who respond to treatment at 16 weeks discontinue at the same constant rate for both bimekizumab and ixekizumab, which is applied in all subsequent cycles.
- The risk of death during each model cycle is assumed to be the same for both treatments, which is the age- and sex-matched mortality risks in the general population (from UK life tables) with a standardised mortality rate (SMR) for patients with psoriatic arthritis applied.
- The model only considers drug acquisition costs. Costs related to drug administration, subsequent treatments, monitoring and disease management, and adverse events are assumed to be equivalent for both treatments and are excluded from the base case analysis. Clinical advice to the EAG was that drug administration, subsequent treatments, monitoring and disease management, and adverse events are likely to be equivalent for bimekizumab and ixekizumab. Therefore, the EAG considers it appropriate that these costs are not included in the model.

The EAG notes these assumptions were previously accepted by the Appraisal Committee for the cost-comparison appraisal of risankizumab for psoriatic arthritis (TA803).[25]

5.1.3 Model parameters

5.1.3.1 PsARC response

In the base case cost comparison models, the company uses the PsARC response from the bimekizumab estimates from their NMA analyses (CS Appendix D) for both treatment arms. The PsARC response rate for the b/tsDMARD experienced population for bimekizumab is 0.85 and for the TNFi-CI population is 0.83 (CS Table 33). Bimekizumab had a higher estimated PsARC response than for ixekizumab (PsARC response: 0.67 for b/tsDMARD experienced; 0.7 for TNFI-CI). CS Figure 14 and 15 show the forest plots for PsARC for bimekizumab vs ixekizumab. According to these plots, bimekizumab is statistically superior to ixekizumab, with regard to PsARC response.

The assumption of equal response in both treatment arms may over-estimate the cost for ixekizumab as more patients would continue to receive treatment using the PsARC response from bimekizumab. The company conducted a scenario analysis using the PsARC response from ixekizumab. We provide a scenario analysis where the PsARC response is taken to be the average response of bimekizumab and ixekizumab.

5.1.3.2 Discontinuation

An equal probability of 16.5% discontinuation per year was assumed across both treatment arms. The CS states that this is consistent with previous technology appraisals TA220, [40] TA340,[41] TA433, [42] TA445,[7] TA537, [10] TA768[13] and cost-comparison TA803.[2] The EAG agrees with the company's approach to discontinuation and its consistency with previous appraisals.

5.1.3.3 Mortality

The model uses general population mortality rates, adjusted for the age and sex of the modelled cohort (England and Wales 2020, ONS 2020). These mortality rates were further adjusted using a SMR of 1.05 to account of a higher risk of death in patients with psoriatic arthritis than the general population. The company tested the impact of excluding the SMR of 1.05 in scenario analysis (CS Table 37 and 38).

The EAG notes that the company does not appear to have used the latest version of mortality from ONS, using the mortality tables from 2017-2019, rather than those from 2018-2020. This is considered a minor issue and has not been addressed by the EAG in exploratory analyses.

5.1.3.4 Costs

The CS reports the dosing assumptions and list prices for the calculation of acquisition costs for bimekizumab and ixekizumab in CS Table 32. We summarise the key assumptions in Table 4 below.

Table 4 Dosing and list prices for bimekizumab and ixekizumab

Therapy (dose)	**Induction**		**Maintenance (doses per year)**	**Price per dose**
	Duration	Doses		
Bimekizumab (1 x 160 mg)	N/A	N/A	13.0	List price £1,221.50; PAS price [redacted]
Ixekizumab (1 x 80 mg)	4 weeks	2	13.0	£1,125

Source: Data extracted by the EAG from information in CS Table 32
NA, not applicable. See confidential addendum to EAG report for ixekizumab PAS prices and analyses

The dosing schedule for bimekizumab and ixekizumab is similar. Ixekizumab has an initial induction dose of two 80mg SC injections whereas bimekizumab does not have an induction dose.

Psoriatic arthritis often occurs concomitantly with plaque psoriasis. The recommended dose of bimekizumab for adult patients with moderate to severe plaque psoriasis is 320mg (two SC injections of 160mg each) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter. For patients with psoriatic arthritis and concomitant moderate to severe plaque psoriasis, the ixekizumab dosing regimen is the same as for plaque psoriasis: 160mg SC injection (two 80mg injections) at week 0, followed by 80mg (one injection) at weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80mg (one injection) every four weeks.

Our clinical expert advised us that most patients with psoriatic arthritis and plaque psoriasis have less severe psoriasis and would likely receive methotrexate treatment for the psoriasis. In our expert's experience, less than 10% of patients have moderate to severe psoriasis and psoriatic arthritis.

In response to clarification question B1, the company explained that previous technology appraisals in psoriatic arthritis have defined moderate to severe psoriasis as body surface area (BSA) >3% affected by psoriasis and PASI score >10. The proportion of patients with BSA ≥3% affected by psoriasis at baseline was 66% in BE COMPLETE and 50% in BE OPTIMAL. The company could not say if this was representative of patients seen in UK clinical practice, because they did not find a definitive source for the proportion of patients with psoriatic arthritis in the UK that have moderate to severe psoriasis.

We explore the effect of using the higher dose (320mg) of bimekizumab and the ixekizumab plaque psoriasis dosing for different proportions of patients with psoriatic arthritis and concomitant moderate / severe psoriasis in scenario analyses. The EAG notes that overweight patients (body weight ≥ 120kg) with moderate to severe plaque psoriasis (including psoriatic arthritis with coexistent moderate to severe psoriasis), who do not achieve complete skin clearance at Week 16, may experience an improved response to treatment after receiving 320mg bimekizumab every four weeks after Week 16 (CS section B.1.2 Table 2). In response to clarification question B2, the company explained that a dose increase is not licensed for overweight patients with psoriatic arthritis only. The company also commented that the dose increase for overweight patients with psoriatic arthritis and moderate to severe psoriasis is covered by TA723, which included ixekizumab as a comparator.

Administration costs were not included in the analysis as there are no expected costs to the NHS for administering SC injections beyond the first administration and there is no difference in resource use associated with drug administration across the two treatments. CS section 4.1 states that bimekizumab is expected to be administered at the patient's home, supported by a home care service provided by UCB Pharma Ltd and this is consistent with current practice for other SC-administered therapies in patients with psoriatic arthritis, such as ixekizumab.

Monitoring costs were not included in the analysis. The CS states that the frequency and costs associated with monitoring of patients receiving bimekizumab is not expected to differ from that of ixekizumab and that this approach is consistent with TA803.

Costs for managing adverse events have not been included in the analysis. The CS states that these are assumed to be similar between the two treatments, as previously assumed in TA803. Further similar adverse events are reported in a post-hoc comparison of treatment emergent adverse events between bimekizumab and the adalimumab reference arm (CS section B 3.10.1.1) and between bimekizumab and ixekizumab in the NMA on serious adverse events (CS section 3.9.4.4).

5.2 EAG model checks

The EAG conducted model checks on the company cost comparison model, including checking the calculations in the Excel spreadsheet. We also double-programmed the model, i.e. constructed a duplicate version to check it produced the same results. We were able to generate the same results as presented in the CS for the base case and scenarios and so we do not believe that the company analyses contain programming errors. The EAG believes that the evidence sources and that the values applied in the executable model are consistent with their original sources. The company has mostly used previous assumptions and approaches used in TA803 and accepted by the Appraisal Committee for that cost comparison appraisal.[2; 25] Therefore, the assumptions used are deemed appropriate by the EAG for this appraisal.

The EAG notes a minor discrepancy in the cost of the ixekizumab loading dose; the original company base case includes this cost for the first five weeks of treatment instead of four. The company corrected the loading dose calculation error in response to clarification question B3 and provided a new version of the model.

5.3 Company cost comparison results

As noted above, the company corrected the cost of ixekizumab in response to clarification question B3. The corrected company base case cost comparison results are presented in Table 5 for b/tsDMARD experienced (clarification question B3 Table 7) and Table 6 for TNFi-CI (clarification question B3 Table 8). The results use the bimekizumab PAS price and the ixekizumab list price with a time horizon of 10 years. The base case results show that bimekizumab has a cost saving of [redacted] compared with ixekizumab for the b/tsDMARD population.

Table 5 Base-case results: b/tsDMARD-experienced – using bimekizumab (PAS price)

Therapy	Total cost	Incremental cost of treatment with bimekizumab vs ixekizumab
Bimekizumab	[redacted]	–
Ixekizumab	£61,734	[redacted]

Source*:* Reproduction of company clarification response B3, Table 7
b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; PAS, patient access scheme.

For the TNFi-CI population, bimekizumab has a cost saving of [redacted] compared to ixekizumab.

The EAG notes that these analyses are not meaningful for decision-making as they do not include the PAS discount for ixekizumab. Results using the PAS prices for bimekizumab and ixekizumab are presented by the EAG in a separate confidential appendix to this report.

Table 6 Base-case results: TNFi-CI – using bimekizumab (PAS price)

Therapy	Total cost	Incremental cost of treatment with bimekizumab vs ixekizumab
Bimekizumab	[redacted]	–
Ixekizumab	£60,519	[redacted]

Source: Reproduction of company clarification response B3, Table 8
PAS, patient access scheme; TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated

The company presents scenario results in clarification question B3 Tables 9 and 10 for the b/tsDMARD experience and TNFi-CI populations, respectively. Decreasing the time horizon

from 10 years to 5 years was associated with the largest difference from the base case results.

5.4 EAG's analyses

To explore uncertainty around clinical efficacy and the dosing for patients with psoriatic arthritis and concomitant psoriasis, the EAG undertook the scenario analyses described in Table 7 and Table 8. The dosing regimens are described in section 5.1.3.4. Using a PsARC response rate that is the average of the bimekizumab and ixekizumab response rates cause the greatest reduction in incremental costs for both patient populations.

Table 7 EAG scenario analyses: b/tsDMARD-experienced patients – using bimekizumab (PAS price)

Scenario	Difference in incremental cost
Base case	[redacted]
PsARC response using the average response of bimekizumab and ixekizumab	[redacted]
66% patients with moderate / severe psoriasis and PsA	[redacted]
50% patients with moderate / severe psoriasis and PsA	[redacted]
10% patients with moderate / severe psoriasis and PsA	[redacted]

Source: EAG's own table
b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; PsA, psoriatic arthritis.

Table 8 EAG scenario analyses: TNFi-CI patients – using bimekizumab (PAS price)

Scenario	
Base case	[redacted]
PsARC response that is the average response of bimekizumab and ixekizumab	[redacted]
66% patients with moderate / severe psoriasis and PsA	[redacted]
50% patients with moderate / severe psoriasis and PsA	[redacted]
10% patients with moderate / severe psoriasis and PsA	[redacted]

Source: EAG's own table
TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated; PsA, psoriatic arthritis.

5.5 List price analyses

The CS includes the PAS discount for bimekizumab, but ixekizumab is also subject to a PAS discount that is not included, so the CS does not provide insight into the actual difference in costs between the two treatments. The company provided list price analyses in CS Appendix M, but these changed slightly following the correction to the model.

The tables below show results of the analyses using the updated model and list prices of both comparators, to illustrate what the difference in costs might be. We provide results with NHS price discounts for bimekizumab and ixekizumab in a separate confidential addendum to this report.

Table 9 and Table 10 show the base case list price results, and scenario analyses are given in Table 11 for the b/tsDMARD-experienced and TNFi-CI populations, respectively. In line with NICE methodological guidance for cost-comparisons,[4] the company did not report a probabilistic sensitivity analysis and all results are deterministic. In addition to the company's scenario analyses, Table 11. include the EAG's scenario analyses (described in section 5.4)

The results show that bimekizumab is more costly than ixekizumab when both treatments are costed at list price.

Table 9 Base case results: b/tsDMARD-experienced – using bimekizumab (list price)

Therapy	Total cost	Incremental cost of treatment with bimekizumab vs ixekizumab
Bimekizumab	£65,808	–
Ixekizumab	£61,734	£4,074

Source: Partly reproduced from CS Appendix M Table 1
b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug

Table 10 Base case results: TNFi-CI – using bimekizumab (list price)

Therapy	Total cost	Incremental cost of treatment with bimekizumab vs ixekizumab
Bimekizumab	£64,489	–
Ixekizumab	£60,519	£3,970

Source: Partly reproduced from CS Appendix M Table 2
Abbreviations: TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated

Table 11 Scenario analyses: b/tsDMARD – experienced and TNFi-CI patients – bimekizumab (list price) vs ixekizumab (list price)

Scenario	Difference in incremental cost	
	b/tsDMARD-experienced patients	TNFi-CI patients
Base-case	£4,074	£3,970
5-year time horizon	£2,608	£2,532
1.5% discount rate for costs	£3,849	£3,749
3.5% discount rate for costs	£3,580	£3,485
IXE PsARC response rate	£3,055	£3,232
PsARC response rate from the b/tsDMARD-naïve NMA	-	£3,516
No SMR adjustment	£4,077	£3,972
IXE 20-week PsARC response assessment	£3,127	£3,017
EAG scenario: PsARC efficacy set to BKZ and IXE mid-point	£3,564	£3,629
EAG scenario: 66% patients with psoriasis and PsA	£5,071	£4,967
EAG scenario: 50% patients with psoriasis and PsA	£4,829	£4,725
EAG scenario: 10% patients with psoriasis and PsA	£4,225	£4,121

Source: Partly reproduced from CS Appendix M Table 3
Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; BKZ, bimekizumab; IXE, Ixekizumab; PsARC, Psoriatic Arthritis Response Criteria; SMR, standardised mortality ratio; PsA, psoriatic arthritis.

5.6 EAG conclusions on the cost comparison

- The structure and key assumptions of the company's cost-comparison model are appropriate, and consistent with previous cost-comparison appraisals (such as risankizumab TA803 for psoriatic arthritis;[2] bimekizumab TA723 for plaque psoriasis[3]
- The company's NMA of bimekizumab to ixekizumab is based on standard NICE DSU methodology
- Sufficient scenario analyses were conducted by the company to explore different assumptions around the model time horizon, discounting, response to treatment and whether a standardised mortality ratio for psoriatic arthritis versus the general population is included or not.
- The EAG agrees with the company's assumptions and choice of modelling methods.

- We identified a minor error in the cost of the ixekizumab loading dose, which the company corrected and provided a new version of the model.
- Results of the company's NMA support the assumption of similar clinical efficacy for bimekizumab and ixekizumab, as measured by findings of statistical significance in the ACR, PASI and PsARC scores; the company base their cost-comparison analyses on PsARC response. Bimekizumab is statistically superior to ixekizumab using this measure and assuming similar response for both treatments may over-estimate the treatment cost of ixekizumab.
- Using the list prices for both treatments indicated bimekizumab is more costly than ixekizumab. This applies for the company's base case analyses and for all company and EAG scenario analyses. Results with PAS discounts for bimekizumab and ixekizumab are shown in a confidential addendum to this report.
- The cost difference between bimekizumab and ixekizumab is most sensitive to using a five year time horizon in the model, and also to varying the proportion of patients with psoriatic arthritis and concomitant psoriasis. Results are not sensitive to whether the standardised mortality ratio for psoriatic arthritis versus the general population is applied or not.

6 EQUALITIES AND INNOVATION

The company does not expect any equality issues (CS section B.1.5); the EAG agrees with this position.

Our clinical expert confirmed that bimekizumab is within the same drug class as ixekizumab and secukinumab. All three drugs bind to IL-17A, but bimekizumab also binds to IL-17F and IL-17AF. Clinical advice to the EAG was that, in theory, there may be extra benefit from this additional binding. However, our expert highlighted that this potential benefit has not been proven in practice, because there is no evidence from head-to-head clinical trials of the anti IL-17 agents.

7 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

The EAG does not identified any critical issues with the evidence provided in the CS that would prevent the appraisal of bimekizumab for treating active psoriatic arthritis proceeding via the cost-comparison approach.

Bimekizumab appears to have similar, and for some clinical effectiveness outcomes better, treatment effects than ixekizumab in both the TNFi-experienced and TNFi-CI populations based on the statistical significance of the NMA results. There were no statistically significant differences in safety between bimekizumab and ixekizumab in the mixed population NMA.

The uncertainties associated with the evidence presented in the CS that we have identified include:

- The populations in the company's key bimekizumab RCTs do not appear to fully represent the decision problem populations. The main reasons for this are that it is unclear if trial participants had previously received two cDMARDs or had a contra-indication to TNF-inhibitors
- The NMA was appropriately conducted but heterogeneity between studies may have been exacerbated by the use of a global network that included a greater number of comparators than relevant to this appraisal. Nevertheless, we found the use of the global network did not bias results.
- For the NMA outcomes where there was an absence of a statistical significantly difference between bimekizumab and ixekizumab, this does not necessarily imply clinical equivalence between the treatments.

The company's cost-comparison analysis has:

- Used a cost-comparison model with an appropriate structure and key assumptions which are consistent with previous cost-comparison appraisals.
- Based their cost-comparison analyses on PsARC response and have assumed similar clinical efficacy. However, because the NMA result shows bimekizumab is statistically superior to ixekizumab for the PsARC outcome, assuming a similar response for both treatments may over-estimate the treatment cost of ixekizumab.

- Demonstrated that using the list prices for both treatments, bimekizumab is more costly than ixekizumab. This applies for the company's base case analyses and for all company and EAG scenario analyses. Results with PAS discounts for bimekizumab and ixekizumab are shown in a confidential addendum to this report.
- Conducted sufficient scenario analyses. The cost difference between bimekizumab and ixekizumab is most sensitive to using a five-year time horizon in the model, and also to varying the proportion of patients with psoriatic arthritis and concomitant psoriasis.

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9 APPENDICES

Appendix 1

The EAG's risk of bias assessment of the BE COMPLETE, BE OPTIMAL and BE ACTIVE RCTs is presented in Table 12 below. We have focused on the PsARC response at Week 16 outcome in our assessment of the BE COMPLETE and BE OPTIMAL trials and PsARC response at Week 12 in our assessment of the BE ACTIVE trial.

Table 12 Company and EAG risk of bias assessments for the BE COMPLETE, BE OPTIMAL and BE ACTIVE RCTs

		BE COMPLETE	BE OPTIMAL	BE ACTIVE
1. Randomisation process	Company	Low risk of bias	Low risk of bias	Low risk of bias
	EAG	Some concerns	Low risk of bias	Some concerns
EAG comment: **BE COMPLETE:** An interactive-voice and web-response system was used for randomisation, with the randomisation schedule pre-prepared by an independent biostatistician.[26] Therefore, adequate randomisation and allocation concealment processes were used. Baseline characteristics were mostly well-balanced between treatment arms, but there were differences between the bimekizumab 160 mg Q4W and placebo arms in use of methotrexate at baseline (45% versus 38%, respectively) and presence of enthesitis (40% versus 27%, respectively).[26] It is unclear whether these differences are sufficient to potentially bias the PsARC response at Week 16 outcome. **BE OPTIMAL:** The same approach to randomisation and allocation concealment was used as described above for the BE COMPLETE trial. Baseline characteristics were well-balanced between trial arms.[27] **BE ACTIVE:** The same approach to randomisation and allocation concealment was used as described for the BE COMPLETE and BE VITAL trials above. There were some baseline characteristic differences between the bimekizumab 160mg Q4W and placebo arms: percentage male (49% versus 57%, respectively), enthesitis (56% versus 48%) and methotrexate as a previous treatment (71% versus 64%). It is unclear whether these differences are sufficient to potentially bias the PsARC response at Week 12 outcome.				

		BE COMPLETE	BE OPTIMAL	BE ACTIVE
2. Deviations from intended interventions	Company	Low risk of bias	Low risk of bias	Low risk of bias
	EAG	Low risk of bias	Low risk of bias	Low risk of bias

EAG comment:

BE COMPLETE: The 16-week trial was double-blinded with matching placebo used,[26; 43] but the study drug was administered to participants subcutaneously by unblinded study personnel who were otherwise only responsible for preparing and recording the drug used (CSR sections 3.2.2 and 3.6.4.1.1[44]), so there was potential for knowledge of the intervention received being revealed. An assessment of this risk of bias domain when there is this uncertainty involves considering if there were any deviations from the intended interventions that arose due to the trial context.[31] Important protocol deviations are reported in the trial paper, Supplementary Table S1, and in the trial CSR, section 7.2.[26; 43; 44] Having reviewed these, we suggest that it is unlikely that any deviations from intended interventions arose because of the trial context and therefore incomplete blinding is likely to result in a low risk of bias on this domain (i.e. performance bias) for this trial.

BE OPTIMAL: Participants and all study personnel, except those administering the study drug, were blinded to treatment assignment. Protocol deviations are listed in CSR section 7.2[45] and the trial paper Supplementary Appendix Table S1,[46] including prohibited concomitant medication use ([redacted] of participants), but we assessed that these were unlikely to have arisen due to the trial context.

BE ACTIVE: Study sites were expected to have a plan in place to maintain the double-blinding of the study.[47] It is unclear how well this was maintained. Additionally, participants in different trial arms received the same number of injections, through the use of placebo when bimekizumab was not required. The CSR states that provisions were in place to prevent the volume of the injection being revealed to participants, but, again, it is unclear how well these procedures would have worked. Study personnel who prepared and administered the study drug were unblinded and so were bioanalytical staff.[47] Protocol deviations are listed in CSR section 7.2[47] and, again, we assessed that these were unlikely to have arisen due to the trial context.

3. Missing outcome data	Company	Low risk of bias	Low risk of bias	Low risk of bias
	EAG	Low risk of bias	Low risk of bias	Low risk of bias

EAG comment:

BE COMPLETE: Based on the proportion of participants who dropped out of the trial reported in CS Appendix D.2 Figure 3 (reported as 98.5% and 94.0% for the bimekizumab 160mg Q4W and placebo arms, respectively) it appears that outcome data were likely to

		BE COMPLETE	BE OPTIMAL	BE ACTIVE
be available for nearly all randomised participants in the trial (but we note that exact numbers of participants with missing data on each of the measured outcomes does not appear to be reported in the CS, trial CSR[43] or trial paper[26]). **BE OPTIMAL:** As for BE COMPLETE, based on the proportion of participants who dropped out of the trial (which ranged from 96.1% to 97.1% depending on the trial arm; CS Appendix D.2 Figure 4) it appears that outcome data were likely available for nearly all randomised participants in the trial. Information on the exact number of participants with missing data on the PsARC outcome at Week 16 does not appear to be available. **BE ACTIVE:** All randomised participants completed the double-blind period up to Week 12.[21] Information on the exact number of participants with missing data on the PsARC outcome at Week 12 does not appear to be available, but based on the numbers completing the study and reported to be included in the PsARC response at Week 12 outcome analyses,[21] the trial appears to be at a low risk of bias on this domain. **Additional EAG comment:** In all the trials, conservative approaches were taken to estimating missing data, also supporting a low risk of bias in this domain.				
4. Measurement of the outcome	Company	Low risk of bias	Low risk of bias	Low risk of bias
	EAG	Low risk of bias	Low risk of bias	Some concerns
EAG comment: **BE COMPLETE:** The method of measuring the PsARC response outcome was appropriate and it is unlikely that assessment of the outcome would have been influenced by knowledge of the intervention. **BE OPTIMAL:** As for the BE COMPLETE trial above, the PsARC response outcome was measured appropriately and it is unlikely that assessment of it was influenced by knowledge of the intervention. **BE ACTIVE:** The method of measuring the PsARC response outcome was appropriate, but due to a lack of clarity about how well blinding was maintained (please see our response to domain 2 above) we have some concerns about whether or not some participants and investigators may have had knowledge of the intervention received that might have biased their judgements when assessing the PsARC response outcome.				
5. Selection of the reported result	Company	Low risk of bias	Low risk of bias	Low risk of bias
	EAG	Low risk of bias	Low risk of bias	Low risk of bias
EAG comment: **BE COMPLETE:** The PsARC response at Week 16 outcome appears to have been analysed in accordance with the pre-specified statistical analysis plan and definition of this outcome.[43]				

		BE COMPLETE	BE OPTIMAL	BE ACTIVE
BE OPTIMAL: The PsARC response at Week 16 outcome appears to have been analysed in accordance with the pre-specified statistical analysis plan and definition of this outcome.[47] **BE ACTIVE:** The PsARC response at Week 12 outcome appears to have been analysed in accordance with the pre-specified statistical analysis plan and definition of this outcome.[34]				
6. Overall bias	Company	Low risk of bias	Low risk of bias	Low risk of bias
	EAG	Some concerns	Low risk of bias	Some concerns
EAG comment: **BE COMPLETE:** The EAG has some concerns about risk of bias due to imbalances between trial arms at baseline in methotrexate use and the presence of enthesitis, although we are unclear if or how these imbalances may potentially impact on outcomes. **BE OPTIMAL:** We assessed this study as being at an overall low risk of bias. **BE ACTIVE:** The EAG has some concerns about imbalances in some baseline characteristics between treatment arms (percentage male, enthesitis and previous methotrexate treatment), but it is unclear if or how these imbalances may potentially impact on the PsARC outcome. In our opinion, there is also a lack of clarity in how well blinding procedures worked, resulting in us judging that there is a risk of detection bias on the PsARC outcome.				

Source: Table compiled by the EAG using information in the CS, and trial CSRs[34; 43; 47] and papers.[21; 26; 27]

Note. The company did not provide comments to support their risk of bias judgements.
CS, company submission; CSR, clinical study report; EAG, External Assessment Group; PsARC, Psoriatic Arthritis Response Criteria; Q4W, every 4 weeks.

Appendix 2

Comparison of treatment experience in the bimekizumab and ixekizumab RCTs

RCT, intervention (NMA included in)	Description of treatment experience	EAG notes
BE ACTIVE, bimekizumkab (TNFi-experienced NMA and TNFi-CI NMA)	Participants could have been exposed to one prior TNF inhibitor treatment. Prior cDMARD treatment not reported (current cDMARDs permitted at stable dose)	Unclear if the prior TNF inhibitor was to treat psoriasis or PsA (all patients had an active psoriatic lesion and/or documented history of psoriasis as well as PsA). Those patents without prior exposure to a TNF inhibitor are not described as having a contraindication to TNFi treatments.
BE COMPLETE, bimekizumkab (TNFi-experienced NMA)	Participants had been treated with either one or two prior TNF inhibitors. Prior cDMARD treatment not reported (current cDMARDs permitted at stable dose)	The prior TNF inhibitor therapy could have been for either PsA or psoriasis (all patients had an active psoriatic lesion and/or documented history of psoriasis as well as PsA)
SPIRIT-P2, ixekizumab (TNFi-experienced NMA)	Participants had been treated with one or more cDMARDs and had prior treatment with either one or two TNF inhibitors.	Unclear if the prior TNF inhibitor was to treat psoriasis or PsA (all patients had an active psoriatic lesion and/or documented history of psoriasis as well as PsA).
BE OPTIMAL, bimekizumkab (TNFi-CI NMA)	No current or previous exposure to any biologics for the treatment of PsA or psoriasis.	These patients are not described as having a contraindication to TNFi treatments
SPIRIT-P1, ixekizumab (TNFi-CI NMA)	No previous treatment with biologic agents for plaque psoriasis or PsA.	These patients are not described as having a contraindication to TNFi treatments

Source: EAG compiled table, using information sourced from the trial publications
cDMARD, conventional disease-modifying anti-rheumatic drug; NMA, network meta-analysis; PsA, psoriatic arthritis; TNF, Tumour necrosis factor alpha; TNFi-CI, Tumour necrosis factor alpha inhibitor-contra indicated.