NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bimekizumab for treating active psoriatic arthritis [ID4009]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Bimekizumab for treating active psoriatic arthritis [ID4009]

Contents:

The following documents are made available to stakeholders:

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

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

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Psoriasis and Psoriatic Arthritis Alliance
   b. Psoriasis Association

4. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre

5. **External Assessment Group response to factual accuracy check of EAR**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost-comparison appraisal

Bimekizumab for treating active psoriatic arthritis [ID4009]

Document B

Company evidence submission

30th May 2023

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ID4009_Bimekizumab in PsA_CC_Document B	1	Yes	30th May 2023

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse event
b/tsDMARD	Biological/targeted synthetic disease-modifying anti-rheumatic drug
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	Biological disease-modifying anti-rheumatic drug
BNF	British National Formulary
BSA	Body surface area
BSR	British Society for Rheumatology
CASPAR	Classification Criteria for Psoriatic Arthritis
CC	Cost comparison
CCI	Charlson Comorbidity Index
cDMARD	Conventional disease-modifying anti-rheumatic drug
CI	Confidence interval
CrI	Credible Interval
DAPSA	Disease Activity Index in PsA
DAPSA-LDA	Disease Activity Index in PsA-Low Disease Activity
DIC	Deviance information criterion
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying anti-rheumatic drug
DSU	Decision Support Unit
ERG	Evidence Review Group
EULAR	European Alliance of Associations for Rheumatology
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FTA	Fast track appraisal
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HADS	Hospital Anxiety and Depression Scale
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – Disability Index
HRQoL	Health-related quality of life
hs-CRP	High sensitivity-C reactive protein
HTA	Health Technology Assessment
IBD	Inflammatory bowel disease
IL-12/23i	Interleukin-12/23 inhibitor
IL-17Ai	Interleukin-17A inhibitor
IL-23	Interleukin-23 inhibitor
IMP	Investigational medicinal product
IR	Inadequate response
JAGS	Just Another Gibbs Sampler
JAKi	Janus kinase inhibitor
LDA	Low disease activity
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index

Abbreviation	Definition
MACE	Major adverse cardiac event
MAPP	Multinational Assessment of Psoriasis and Psoriatic Arthritis
MCS	Mental Component Summary
MDA	Minimal disease activity
MI	Multiple imputation
mNAPSI	Modified nail psoriasis severity index
MTA	Multiple technology appraisal
MTX	Methotrexate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OLE	Open-label extension
ONS	Office for National Statistics
OR	Odds ratio
PAS	Patient access scheme
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PDE-4i	Phosphodiesterase-4 inhibitors
PhGA	Physician's Global Assessment
PRO	Patient reported outcome
PsA	Psoriatic arthritis
PsAID	Psoriatic Arthritis Impact of Disease
PsAQoL	Psoriatic arthritis quality of life
PsARC	Psoriatic Arthritis Response Criteria
PSO	Psoriasis
PtAAP	Patient's assessment of arthritis pain
PtGA	Patient's Global Assessment
PY	Participant-years
QoL	Quality of life
QXW	Every X weeks
RCT	Randomised controlled trial
RR	Risk ratio
RS	Randomised set
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short Form-36
SFU	Safety follow up
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SoC	Standard-of-care
STA	Single technology appraisal

Abbreviation	Definition
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
THIN	The Health Improvement Network
TJC	Tender joint count
TNF	Tumour necrosis factor alpha
TNFi	Tumour necrosis factor alpha inhibitor
TNFi-CI	Tumour necrosis factor alpha-contra indicated
TNFi-IR	Tumour necrosis factor alpha-inadequate responders
TSD	Technical support document
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drugs
ULN	Upper limit of normal
VAS	Visual analogue scale
vdHmTSS	Van der Heijdes modified Total Sharp Score
VLDA	Very low disease activity

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

Psoriatic arthritis (PsA) is a chronic, life-long, progressive systemic inflammatory condition with varied clinical manifestations and an early age of onset

- PsA, a musculoskeletal condition, is the most common subtype of peripheral spondyloarthritis (1), however there is significant overlap between axial and peripheral subtypes (1, 2)
- For most United Kingdom (UK) patients, the onset of PsA is between 30 and 60 years (3), and peripheral joint disease is progressive (4). Multiple lines of therapy, and therapies with different mechanisms of action are required for long-term control of the disease (5)
- Key factors playing a role in the pathogenesis of PsA include cytokines such as interleukin (IL)-17 (produced as IL-17A/A homodimer, IL-17F/F homodimer, or IL-17A/F heterodimer), IL-23, and tumour necrosis factor alpha (TNF), driving local synovial and skin inflammation, and bone remodelling (6)
- The clinical manifestations of PsA are heterogenous, broadly classified into musculoskeletal, and non-musculoskeletal manifestations
  - Musculoskeletal manifestations include peripheral arthritis (7), dactylitis (i.e. “sausage digit”), and enthesitis (8, 9)
  - Non-musculoskeletal manifestations include:
    - Skin and nail psoriasis: up to 41% of patients with psoriasis (PSO) develop concomitant PsA (10-12). PSO frequently precedes development of PsA (~85% of patients, mean interval of 10 years), however, ~15% of patients may have simultaneous development of skin and joint disease or joint disease that precedes PSO (13)
- PsA is also associated with other co-morbidities such as uveitis, and inflammatory bowel disease (14)

PsA is associated with significant clinical, humanistic, and economic burden

- In the UK, the overall prevalence of PsA is estimated to be 0.19% (3)
- Patients with PsA experience debilitating symptoms including pain, stiffness, and swelling in one or more peripheral joints (15), PSO-associated symptoms (dry, itchy, and sore skin patches (16)), and fatigue (17, 18)
- There is a significant association between joint damage and disability, and physical function (19, 20), with the greatest physical impact among patients with enthesitis or dactylitis compared with all patients with PsA (21)

- Key symptoms of PsA contributing to reduced health-related quality of life (HRQoL) include joint disease, pain, fatigue, and skin disease (21-24)
- Patients with PsA and substantial skin involvement (PSO body surface area [BSA] >3%) report higher disease burden, and worse patient-reported outcomes than those with less substantial skin involvement (PSO BSA ≤3%) (25, 26)
- The relationship between PsA and co-morbid conditions is complex, with several also considered to be manifestations as well as risk factors. These co-morbidities also have a significant impact on patient quality of life (QoL) (27)
- Patients with PsA are also at an increased risk of developing psychological co-morbidities (28)
- The effect of PsA on patients' physical and mental health can be seen early in the course of the disease. Patients with early PsA (defined as disease manifestation <2 years before first rheumatology visit (29)) have significantly lower Short-form 36 (SF-36) domain scores, and component summaries (mental, and physical) compared with a matched, age-adjusted general population ($p<0.05$ for all domains) (30), with HRQoL remaining significantly impaired at 5-years follow-up
- The mean annual per patient healthcare cost of PsA in the UK[a] (excluding medication costs) is estimated to be £1,586, including tests, accident and emergency visits, primary and secondary care consultations, and admitted care (31). Total healthcare costs are highly correlated with functional status, mainly driven by the cost of secondary care consultations (31)

Treatments for PsA include conventional disease-modifying anti-rheumatic drugs (cDMARD), biologic DMARDs (bDMARD), and targeted synthetic DMARDs (tsDMARD) (32)

- The aims of treatments for PsA are to improve the signs and symptoms of disease, inhibit the structural progression of joint damage, improve functional capacity and QoL, and reduce pain (33). Recent Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and British Society of Rheumatology (BSR) PsA guidelines recommend that, where possible, treatment should be selected to address all active domains of disease with the goal to achieve the lowest level of disease activity in all domains (34, 35)
- Achieving higher treatment targets, such as minimal disease activity (MDA), Psoriasis Area and Severity Index (PASI)100, American College of Rheumatology (ACR)50 or ACR70, results in a greater improvement in patients' HRQoL (36, 37)

[a] Using 2012/2013, and 2014/2015 NHS reference costs datasets for hospital episodes (31).

- Current treatments result in varying levels of effectiveness on the different disease manifestations (35); clinical guidelines use a 'manifestation-based' approach for treatment recommendations (34, 35)

Despite currently available treatments for patients with PsA who are b/tsDMARD-experienced or b/tsDMARD-naïve, there is an unmet need for additional treatment options with a rapid, effective, and sustained response, and improved patient QoL

- Data from clinical studies show that over 50% of TNF-inhibitor (TNFi)-experienced (38-47), and bDMARD-naïve patients (38-40, 44, 46-60) treated with current advanced therapies fail to achieve American College of Rheumatology (ACR)50, PASI90, or PASI100 at Week 24, and therefore joint and skin manifestations are not treated optimally
- Uncontrolled disease can result in irreversible joint damage, and functional impairment (61). Up to 85% of patients with PsA do not achieve MDA or low disease activity in clinical practice (62)
- Several studies have reported that patients switching to a second TNFi have significantly poorer response and/or measures of disease activity compared with non-switching patients (63-65). Furthermore, a systematic literature review (SLR) of randomised controlled trials (RCTs) investigating IL-17A inhibitors and IL-12/23 inhibitors for patients who were intolerant to or have responded inadequately to TNFi therapy, reported that although these therapies are still efficacious in these patients, their efficacy is attenuated compared with TNFi-naïve patients (66)
- Among patients with PsA, 90% express unhappiness with current treatment options, with a need for better therapies (21), and 40–60% report moderate to severe disease while being treated with advanced therapies, including biologics (67)
- Poor treatment response in PsA is associated with a substantial negative impact on patients (68)

Bimekizumab is the only available humanised immunoglobulin monoclonal antibody that binds to both IL-17F in addition to IL-17A in order to inhibit the IL-17 pathway, a pivotal driver of inflammation (69, 70)

- IL-17A and IL-17F are cytokines with overlapping biology that are independent pivotal drivers of inflammation and pathological bone formation in PsA (71-74). Hence, the inhibition of IL-17F in addition to IL-17A may lead to greater resolution of inflammation than inhibition of IL-17A alone, as demonstrated by *in vitro* disease models (72-74)

- Bimekizumab is anticipated to be used in clinical practice for the treatment of adult patients with active PsA 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:
    - They have had two cDMARDs and at least one bDMARD, or
    - TNFi are contraindicated but would otherwise be considered (as described in the National Institute for Health and Care Excellence's [NICE] technology appraisal guidance on etanercept, infliximab, and adalimumab for the treatment of PsA (75)).

B.1.1 Decision problem

Bimekizumab (Bimzelx®), alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis (PsA) in adults who have had an inadequate response (IR) or who have been intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs) (Appendix C).

This submission focusses on part of the technology's marketing authorisation for adult patients with active PsA 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
  - They have had two conventional DMARDs (cDMARD) and at least one biological-DMARD (bDMARD), or
  - Tumour necrosis factor inhibitors (TNFi) are contraindicated but would otherwise be considered (as described in the National Institute for Health and Care Excellence's [NICE] technology appraisal guidance on etanercept, infliximab, and adalimumab for the treatment of PsA (75)).

The decision problem addressed in this submission, including the justification for selecting the proposed comparator ixekizumab for cost-comparison, is provided in Table 1, which also outlines any differences from the NICE final scope (76).

Table 1: The decision problem

	Final scope issued by NICE (76)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope

Population	Adults with active PsA	Adult patients with active PsA 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
		  ○ They have had two cDMARDs and at least one bDMARD, or
		  ○ 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 PsA (75))
			This population is narrower than the NICE guidance language for the proposed comparator ixekizumab (TA537 (77); i.e. ixekizumab is recommended for patients after two cDMARDs or for patients who have had an inadequate response or stopped responding to TNFi or who are TNFi-CI). The guidance for ixekizumab was produced before biosimilar adalimumab pricing was available for health technology assessment. The proposed position of bimekizumab aligns with the most recent NICE recommendations in PsA (TA768 [upadacitinib (78)], TA815 [guselkumab (79)]), both of which occurred after the availability of adalimumab biosimilar. These latest treatments are approved for patients who have had two cDMARDs and at least one bDMARD, or who are TNFi-CI. NHS advisers indicated that the use of IL-17is within the NHS is more consistent with upadacitinib and guselkumab NICE guidance (78, 79) than with ixekizumab (77) NICE guidance (80). This is also consistent with market research data, which shows that IL17Ais have a lower market share in b/tsDMARD-naïve patients ([redacted]), with a [redacted] market share in b/tsDMARD-experienced patients. The market share for IL-17is is higher in the TNFi-CI population ([redacted]) versus the full b/tsDMARD-naïve population (81)

Intervention	Bimekizumab	Bimekizumab	N/A
Comparator(s)	For people who have only received 1 previous cDMARD: • cDMARDs For people whose disease has not responded adequately to at least 2 cDMARDs:	Ixekizumab (IL-17Ai)	Ixekizumab is the most relevant comparator in the scope: • In a UK advisory board (N=7), clinical experts considered IL-17Ais to be the most appropriate comparators for a cost-comparison submission for bimekizumab (82) • In the submission NMA, bimekizumab has statistically superior or similar efficacy vs

	Final scope issued by NICE (76)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• bDMARDs (with or without methotrexate including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, ixekizumab, and secukinumab) • Apremilast • Tofacitinib • Upadacitinib For people whose disease has not responded adequately to cDMARDs and 1 or more TNFi: • Ustekinumab • Secukinumab • Certolizumab pegol • Tofacitinib • Ixekizumab • Best supportive care For people in whom TNFi are contraindicated or not tolerated: • Ustekinumab • Secukinumab • Ixekizumab • Tofacitinib • Guselkumab • Upadacitinib • Best supportive care For people whose disease has not responded adequately to cDMARDs and 1 or more		ixekizumab on joint manifestations (ACR20, ACR50, ACR70, PsARC), extra-articular manifestations (PASI75, PASI90, PASI100, enthesitis, dactylitis), functional capacity/QoL (HAQ-DI, pain VAS, SF-36 PCS, SF-36 MCS), and composite measures (MDA, VLDA) (Section B.3.9.4 & Appendix D) • In the decision problem population, ixekizumab has a market share in b/tsDMARD-experienced patients of [redacted], and an estimated market share in TNFi-CI patients of [redacted] (81) • Bimekizumab was approved for the treatment of moderate to severe plaque PSO in TA723, with a cost-comparison vs ixekizumab finding bimekizumab to have similar health benefits and costs to ixekizumab (82). In PsA, ixekizumab has an additional loading dose, while bimekizumab does not (83) • Bimekizumab and ixekizumab display equivalent affinity for blocking IL-17A i*n vitro, a*nd bimekizumab is reported to be markedly more potent than secukinumab at blocking IL-17A (70) • An NMA shows in a TNFi-experienced population, bimekizumab is statistically superior vs ixekizumab for ACR20, PASI100, PsARC, and enthesitis resolution, with no significant difference in ACR50, ACR70, PASI75, PASI90, MDA, VLDA, HAQ-DI, SF-36 MCS, SF-36 PCS, dactylitis resolution, and pain VAS (Section B.3.9.4.2 & Appendix D). In a TNFi-CI population, bimekizumab was statistically superior vs ixekizumab for ACR70, and PsARC, with no significant difference in ACR20, ACR50, PASI75, PASI90, and PASI100 (Section B.3.9.4.3). In a mixed population of TNFi-experienced, and b/tsDMARD-naïve patients, bimekizumab and ixekizumab were similar for

	Final scope issued by NICE (76)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	bDMARDs, or for whom these are not tolerated: • Guselkumab • Upadacitinib • Best supportive care For people whose disease has not responded adequately to 2 cDMARDs and 1 or more bDMARDs, or for whom these are not tolerated and have moderate to severe psoriasis: • Risankizumab • Best supportive care		SAEs, discontinuation, and discontinuation due to AEs (Section B.3.9.4.4.1) Other comparators are less relevant than ixekizumab • The *in vitro* affinity of ixekizumab for IL-17A is approximately 50–100 times higher than that of secukinumab (84) • The systematic review identified no published PsARC data between Week 12 and 24 in the TNFi-experienced or b/tsDMARD-naive population for secukinumab. Only Week 24 data in a mixed population were identified. Secukinumab does not have sufficient data to be compared with bimekizumab in either of the populations of the NMA: TNFi-experienced patients, and TNFi-CI patients • IL-23is are generally less effective in joints than bimekizumab and ixekizumab (as measured by ACR20, ACR50, and ACR70 [Section B.3.9.4]), have a different mechanism of action, and have less market share in the decision problem population (81) • JAKis are not considered to be appropriate comparators, as serious safety concerns have been raised regarding JAKis by the MHRA (85), EMA (86), and FDA (87). In a UK advisory board (N=7), a clinical expert noted that the FDA ruling on JAKis may have made clinicians more cautious of using JAKis (80). Furthermore, JAKi have a lower market share than IL-17Ais (81)

	Final scope issued by NICE (76)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes†	The outcome measures to be considered include: • Disease activity • Functional capacity • Disease progression • Periarticular disease (for example enthesitis, tendonitis, dactylitis) • Axial outcomes • Mortality • Adverse effects of treatment • HRQoL	• Disease activity: ACR20/50/70 response, PASI75/90/100 response, composite ACR50+PASI100 response, PsARC response, MDA response, VLDA response, mNAPSI resolution • Functional capacity: HAQ-DI change from baseline • Disease progression: vdHmTSS change from baseline, and proportion of patients with no radiographic progression (vdHmTSS change from baseline ≤0.5%) • Periarticular disease: enthesitis resolution (LEI), dactylitis resolution (LDI) • Axial outcomes: BASDAI change from baseline • Adverse effects of treatment: AEs, including deaths • HRQoL: SF-36 PCS change from baseline	• Mortality was not included in the cost-comparison, as: ○ No trials have demonstrated an effect on mortality from treatment because of insufficient follow-up to measure mortality in a chronic condition like PsA (88, 89) ▪ In TA803, the ERG's clinical advisor agreed that most PsA studies have a short-follow up duration and do not capture effects on survival, typically focussing on capturing differences in disease activity (88). In TA537, the ERG also agreed short-term trials are unlikely to demonstrate any effect of treatment on mortality (89) ▪ The time horizon of the cost-comparison would not be expected to show a differential effect on mortality
Subgroups to be considered	None specified	Patients with active PsA: • who are TNFi-CI • who are bDMARD-IR	The data presented in this submission reflects these populations. They were assessed in order to evaluate consistency of response across patients within the proposed population

†Definitions of trial outcomes are provided in Appendix K.

Abbreviations: ACR, American College of Rheumatology; AE, adverse event; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biologic disease-modifying anti-rheumatic drug; bDMARD-IR, biological disease-modifying anti-rheumatic drug-inadequate responders; b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; DMARD, disease-modifying anti-rheumatic drug; EMA, European Medicines Agency; ERG, external review group; FDA, U.S. Food and Drug Administration; HAQ-DI, Health Assessment Questionnaire-Disability Index; HRQoL, health-related quality of life; IL-17Ai, interleukin-17A inhibitor; IL-23i, interleukin-23 inhibitor; JAKi, Janus kinase inhibitor; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; MHRA, Medicines and Healthcare products Regulatory Agency; mNAPSI, modified Nail Psoriasis Severity Index; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; PSO, psoriasis; QoL, quality of life; SAE, serious adverse event; SF-36 MCS, Short form-36 mental component summary; SF-36 PCS, Short form-36 physical component summary; TNFi, tumour necrosis factor alpha inhibitor; TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated; UK, United Kingdom; VAS, visual analogue scale; vdHmTSS, van der Heijde Modified Total Sharp Score; VLDA, very low disease activity.

In this submission, terminology used to describe the populations of interest differs slightly between sections, in order to retain accuracy and reflect the true population studied.

Currently, the majority of clinical trials in a naïve population refer to patients as TNFi-naïve or bDMARD-naïve, as they were designed either prior to the availability of targeted synthetic-DMARDs (tsDMARDs; Janus kinase inhibitors [JAKi], phosophodiesterase-4 inhibitors [PDE-4i]), or were limited for use for patients with inadequate response to at least one bDMARD, or when a bDMARD was not appropriate (90). The majority of clinical trials in an experienced population refer to patients as TNFi-experienced or TNFi-IR, as they were designed when standard-of-care (SoC) was to commence therapy with a TNFi rather than other bDMARDs (90, 91). Recent treatment guidelines no longer distinguish between bDMARDs (TNFi, interleukin (IL)-12/23i, IL-17i, IL-23i) or tsDMARDs (JAKi, PDE-4i) as first-line therapies after inadequate response or intolerance to cDMARDs (35, 90).

- In Section B.1, in order to reflect the evolving clinical guidelines, patients are referred to as **b/tsDMARD-experienced**, or **b/tsDMARD-naïve.**
- In Section B.3, the terminology used for studies included in the Phase 3 clinical trial programme for bimekizumab aligns with the patient populations included in the studies
    - The experienced patients are referred to as **TNFi-IR**, as per the BE COMPLETE inclusion criteria (Section B.3.3.1.2)
    - The naïve patients are referred to as **bDMARD-naïve**, as per the BE OPTIMAL inclusion criteria (Section B.3.3.1.2).
- In Section B.3, the terminology used to describe the NMA aligns with the included studies:
    - **TNFi-experienced**, for all studies eligible for inclusion, the study populations included TNFi-exposed patients, or patients with an inadequate response or intolerance to at least one prior TNFi-therapy
    - **TNFi-contraindicated** (TNFi-CI), uses studies from the b/tsDMARD-naïve network, but TNFi treatments have been removed
    - **Mixed population** of patients who are b/tsDMARD-naïve or TNFi-experienced.
- In Section B.4, the terminology aligns with the proposed positioning of bimekizumab:
    - **b/tsDMARD-experienced**
    - **TNFi-CI**.

B.1.2 Description of the technology being evaluated

The technology being appraised in this submission (bimekizumab) is described in Table 2. The draft summary of product characteristics (SmPC) and the United Kingdom (UK) public assessment report are provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Bimekizumab (Bimzelx®)
Mechanism of action	Bimekizumab is the first biologic designed to selectively inhibit both IL-17A and IL-17F (70), cytokines with overlapping biology that are independent pivotal drivers of inflammation and pathological bone formation in PsA (71-74). Hence, the inhibition of IL-17F in addition to IL-17A may lead to greater resolution of inflammation than inhibition of IL-17A alone, as demonstrated by *in vitro* disease models (72-74). As both IL-17A and IL-17F can be produced independently of IL-23, inhibition of IL-23 can only partially suppress IL-17-mediated inflammation (74, 92)
Marketing authorisation/CE mark status	Bimekizumab does not yet have marketing authorisation for the indication in this submission. A regulatory submission was made to the EMA in 08/2022. Submission to MHRA was made in 05/2023 using the European Commission Decision Reliance Procedure. CHMP positive opinion was received on 26/04/2023 (93) and MHRA regulatory approval is expected as early as [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Bimekizumab is indicated for the treatment of moderate to severe plaque PSO in adults who are candidates for systemic therapy (94) Bimekizumab, alone or in combination with MTX, is anticipated to be licensed for the treatment of active PsA in adults who have had an inadequate response or who have been intolerant to one or more DMARDs (Appendix C) Contraindications: • Hypersensitivity to the active substance or to any of the excipients (glycine, sodium acetate trihydrate, glacial acetic acid, polysorbate 80, water for injections) • Clinically important active infections (e.g. active tuberculosis)
Method of administration and dosage	The recommended dose for adult patients with active PsA is 160 mg (given as one SC injection of 160 mg) every 4 weeks (Appendix C) Consideration should be given to discontinuing treatment in patients who have shown no improvement by 16 weeks of treatment (Appendix C) NICE approval has already been received for adult patients with moderate to severe plaque PSO who are candidates for systemic therapy (82). For patients who have PsA with coexistent moderate to severe plaque PSO†), the recommended dose is the same as for plaque PSO (320 mg [given as 2 SC injections of 160 mg each] at Weeks 0, 4, 8, 12, 16, and Q8W, thereafter). After 16 weeks, regular assessment of efficacy is recommended and if a sufficient clinical response in joints cannot be maintained, a switch to 160 mg Q4W can be considered. For overweight patients with plaque PSO ([including

	PsA with coexistent moderate to severe PSO] body weight ≥120 kg) who did not achieve complete skin clearance at Week 16, 320 mg Q4W after Week 16 may further improve treatment response (Appendix C). As noted in TA723 (82), the proportion of the moderate to severe PSO population weighing above 120 kg is expected to be small
Additional tests or investigations	Not required
List price and average cost of a course of treatment (excluding VAT)	The list price is £2,443 per pack of two pre-filled pens or pre-filled syringes containing 160 mg/mL solution for injection (hospital only) (95); £1,221.50 per 160 mg/ml injection The average length of a course of treatment of bimekizumab is approximately 3 years, based on a 16.50% annual discontinuation rate. This is associated with a cost of £61,500 at the list price based on a dosing schedule of 160 mg Q4W
Patient access scheme/commercial arrangement (if applicable)	Bimekizumab is subject to a confidential simple discount PAS price at a cost of £[redacted] ([redacted] discount off list price) per 160 mg/mL injection pre-filled syringe or pre-filled pen (excl. VAT)

†The moderate to severe PSO population in the clinical trials was defined as PASI score ≥12 and BSA affected by PSO ≥10% and IGA ≥3 on a 5-point scale (96-98), and NICE define severe PSO in TA723 guidance as total PASI ≥10 and a DLQI of ≥10.
Abbreviations: BSA, body surface area; cDMARD, conventional disease-modifying anti-rheumatic drug; CHMP, Committee for Medicinal Products for Human Use; DLQI, Dermatology Life Quality Index; DMARD, disease-modifying anti-rheumatic drug; EMA, European Medicines Agency; IGA, Investigator's Global Assessment; IL-17A, interleukin-17A; IL-17F, interleukin-17F; IL-23, interleukin-23; MHRA, Medicines and Healthcare products Regulatory Agency; MTX, methotrexate; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PSO, psoriasis; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SmPC, summary of product characteristics; VAT, value-added tax.

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

B.1.3.1 Disease overview and patient burden

Spondyloarthritis refers to a group of interrelated, systemic, chronic, rheumatic inflammatory diseases. Affected sites include entheses (i.e. the attachment points for ligaments and tendon to bone), the axial skeleton (including the spine and sacroiliac joints of the pelvis), peripheral joints, the skin, and various other non-musculoskeletal structures (e.g. the gut, eye and aortic valve) (99). Based on the main clinical manifestation, spondyloarthritis is classified into two major subtypes: axial or peripheral (1). PsA, a musculoskeletal condition, is the most common subtype of peripheral spondyloarthritis (1). However, there is significant overlap between axial, and peripheral subtypes, with patients with PsA often experiencing axial manifestations (e.g. sacroiliitis, and spondylitis) (1, 2).

PsA is a chronic, life-long condition, with an early age of onset (between 30–60 years for most UK patients (3)). Multiple lines of therapy, and therapies with different mechanisms of action are required for the long-term control of PsA (5).

PsA occurs as a result of genetic predisposition and environmental triggers, activating the innate and adaptive immune system (100). This activation results in the expansion of immune cells which cause inflammation and damage to skin, joints, and entheses. Key factors playing a role in the pathogenesis of PsA include cytokines such as interleukin-17 (IL-17; produced as IL-17A/A homodimer, IL-17F/F homodimer, or IL-17A/F heterodimer), IL-23, and tumour necrosis factor alpha (TNF) driving local synovial and skin inflammation, and bone remodelling (6). Importantly, elevated levels of IL-17A and IL-17F have been shown in both skin and synovium from patients with PsA, with IL-17F levels elevated to an even greater extent than IL-17A, indicating a pathogenic role in PsA (101, 102). IL-17A and IL-17F are independent pivotal drivers of inflammation and pathological bone formation (71-74). The contribution of these pathogenic mechanisms may vary across different tissues, such as the synovium and the skin (103). Treatments targeting IL-23 and IL-17 inflammatory pathways in patients with PsA reduce symptoms and disease progression (104), highlighting the key role these cytokines play in the pathogenesis of PsA.

B.1.3.1.1 Disease manifestations and symptoms

The clinical manifestations of PsA are heterogenous and vary between patients, resulting in a burdensome symptom profile across multiple areas of the body owing to the systemic inflammatory nature of PsA. These manifestations can be broadly classified into musculoskeletal (Section B.1.3.1.1.1) and non-musculoskeletal (Section B.1.3.1.1.2).

Five overlapping subtypes of PsA have been described, depending on the pattern of joint involvement (105, 106). These include (105):

- Distal arthritis (which predominantly involves the distal interphalangeal joints of the toes, fingers and thumbs)
- Oligoarticular arthritis (≤4 affected joints, usually with an asymmetrical distribution)
- Polyarticular arthritis (≥5 affected joints)
- Predominant spinal involvement
- Arthritis mutilans (a destructive form of arthritis which results in severe joint and bone damage).

B.1.3.1.1.1 Musculoskeletal manifestations

The main musculoskeletal symptoms of PsA include pain, stiffness, and swelling in one or more peripheral joints (15). Hallmark peripheral musculoskeletal manifestations of PsA include peripheral arthritis (7), and the periarticular manifestations dactylitis (i.e. “sausage digit”) and enthesitis (8, 9). Dactylitis is swelling commonly affecting digits in the feet, but can also affect the hands, and multiple digits simultaneously, often occurring asymmetrically (8, 107). It presents as a tender, erythematous (red), warm digit, or as a swollen, asymptomatic digit (8). Enthesitis (i.e.

inflammation of entheses) causes pain and stiffness, particularly during movement (9, 108). Enthesitis and dactylitis are associated with higher disease activity, and overall disease burden, reduced functional status, greater pain, fatigue, and disability vs patients who have PsA without these features (109). Axial manifestations of PsA primarily involve inflammation between the spinal vertebrae, and inflammation of the sacroiliac joints (7).

Joint damage in PsA is usually measured by X-ray (conventional radiography). Radiographic features of PsA include (110):

- joint erosions
- joint space narrowing
- bony proliferations
- osteolysis (destruction of bone tissue)
- ankylosis (stiffening/immobility of joint due to fusion of bone)
- spur (i.e. bony projections) formation, and
- spondylitis (inflammation leading to fusion of the spine).

Joint damage can also be detected clinically, by identifying deformed, fused, or flail joints (111). Radiographic damage (i.e. joint damage measured by radiography) and functional impairment occurs in up to 47% of patients with PsA, within a median interval of 2 years of PsA onset (112).

In most patients with PsA, peripheral joint disease is progressive (4), and in general, physical functioning in PsA worsens as the number of inflamed joints and disease activity increases (20). The rate of joint damage progression increases when the disease is left untreated (113). In a study of 1,077 patients with PsA, greater damage was observed using clinical and radiographic measures among patients seen in a specialised clinic more than 2 years after diagnosis vs those first seen within 2 years; the patients presenting later had higher rates of axial and peripheral disease ($p=0.02$), radiographic damage ($p<0.0001$), and a higher mean number of damaged joints ($p<0.0001$) (113). In another study, a delay in PsA diagnosis of more than 6 months from symptom onset to first rheumatology visit was associated with poor radiographic outcome, and worse long-term physical function (114).

Notably, certain characteristics are predictive factors for the structural progression of joint damage in PsA, including systemic inflammation (indicated by elevated levels of high sensitivity C-reactive protein [hs-CRP]) (115, 116), and the existence of radiographic damage, where patients with damage are more prone to develop further damage, particularly in the presence of elevated hs-CRP (117). Radiographic damage is also reported to be a prognostic factor of mortality in patients with PsA (118).

Taken together, this highlights the need for early diagnosis and effective treatments early in the treatment pathway to prevent the progression of damage and disability. The recent British Society for Rheumatology (BSR) 2022 guidelines propose the earlier use of b/tsDMARDs after failure of one cDMARD (the use of biologics after one cDMARD is not currently permitted by NICE), for patients with poor prognostic factors, or severe active disease (35). The BSR guidelines cite the CONTROL study, which showed that when comparing dose escalation of MTX with the addition of TNFi in patients with an inadequate response after initial MTX therapy, a significantly higher proportion of patients achieved minimal disease activity (MDA) at Week 16 after introducing adalimumab vs dose escalation of MTX (35, 119). The guidelines also cite the SEAM-PsA study, which compared etanercept with etanercept plus MTX combination therapy, and MTX monotherapy, and demonstrated superiority of etanercept over MTX (35, 120).

B.1.3.1.1.2 Non-musculoskeletal manifestations and other co-morbidities

PsA is also associated with non-musculoskeletal manifestations (including skin and nail psoriasis [PSO]) and other co-morbidities (such as uveitis, and inflammatory bowel disease [IBD]).

B.1.3.1.1.2.1 Psoriasis and nail psoriasis

PSO is an inflammatory skin disease which causes raised, scaly patches, with a prevalence of 1.92% in UK adults (2017) (121); up to 41% of patients with PSO develop concomitant PsA (10-12). PSO frequently precedes development of PsA (in ~85% of patients with PsA, with a mean interval of 10 years), however ~15% of patients may have simultaneous development of skin and joint disease or joint disease that precedes PSO (13). Patients who have PsA with skin involvement experience a variety of PSO-associated symptoms, typically presenting with thick red, scaly patches of skin that can be dry, itchy, and sore (16). Commonly affected areas include the elbows, knees, lower back, face, scalp, hands, and soles of the feet. Patients with PsA and substantial skin involvement (PSO body surface area [BSA] >3%) report higher disease burden, and worse patient-reported outcomes (PROs) than those with less substantial skin involvement (PSO BSA ≤3%) (25, 26). In a quantitative study of adult patients formally diagnosed with PsA and receiving treatment (2-hour online focus group, n=5; 45-minute online interviews, n=234), 30% of patients reported that skin-related symptoms have a greater emotional impact versus joint-related symptoms (26%) (122).

Nail PSO is present in up to 80% of patients with PsA, characterised by pitting (i.e. superficial depressions), onycholysis (detachment of the nail from the nail bed), sublingual hyperkeratosis (a build-up of skin cells underneath the nail), transverse grooves/ridges, and discolouration (123). Symptoms of nail PSO include pain and functional impairment, impacting on daily activities (124, 125). In a large retrospective observational study of 2,042 adults with PSO (38.4% of which had PsA), the 16% of patients with nail PSO reported higher pain, fatigue, and Dermatology Life

Quality Index (DLQI) scores, and were more likely to have anxiety, and depression than those without nail PSO (124).

B.1.3.1.1.2.2 Other co-morbidities

Other co-morbidities associated with PsA include immune-mediated ophthalmic disease in the form of uveitis, and IBDs such as ulcerative colitis, and Crohn's disease (14). Patients may also experience co-morbid cardiovascular disease, metabolic syndrome, diabetes, osteoporosis, mood disorders, fibromyalgia, non-alcoholic fatty liver disease, and obesity (14, 126, 127). The relationship of these co-morbid conditions with PsA is complex; several comorbidities are also considered to be clinical manifestations of PsA, as well as risk factors.

The co-morbidities associated with PsA have a significant impact on patient quality of life (QoL). In a systematic literature review (SLR) of 18 publications investigating co-morbid conditions, across a range of PROs (including EQ-5D, Health Assessment Questionnaire [HAQ], Short-form [SF-36]), fibromyalgia, metabolic syndrome, smoking, and alcohol consumption were found to have a negative impact on overall health-related quality of life (HRQoL) in patients with PsA (27). A higher number of co-morbidities and/or more severe co-morbid conditions were shown to further worsen HRQoL. For example, patients with a Charlson Comorbidity Index (CCI) of 1 or ≥2 vs those with a CCI of 0 reported significantly higher HAQ and Patient's Global Assessment (PtGA) scores ($p<0.001$ and $p=0.021$, respectively). Overall, this study highlighted that more than half of patients with PsA suffer from at least one co-morbid condition, and that HRQoL is impaired in these patients more than in patients with PsA alone.

Patients with PsA are at increased risk of developing psychological co-morbidities. Compared with a matched UK general population, the prevalence of depression is significantly higher among patients with PsA (standardised morbidity ratio: 1.3; $p<0.005$) (128). In another study comparing patients with PsA vs those with PSO without PsA, the rates of both depression and anxiety (defined as a Hospital Anxiety and Depression Scale [HADS] subscale score of ≥8) were higher in patients with PsA (prevalence of depression 22.2% vs. 9.6%, $p=0.002$; anxiety 36.6% vs. 24.4%, $p=0.012$; co-morbid depression and anxiety 17.7% vs. 6.7%, $p=0.002$) (28). Grouping patients into HADS ≤7 (unlikely), HADS 8–10 (possible), and HADS ≥11 (probable), the likelihood of depression or anxiety in patients with PsA was greater with unemployment ($p<0.0001$, and $p=0.02$, respectively), a higher actively inflamed joint count ($p<0.0001$, $p=0.0005$, respectively), and a higher score on the Physician's Global Assessment (PhGA) ($p<0.0001$, $p=0.0009$, respectively) (28). In addition, all PROs were poorer in patients with depression, and anxiety (28).

B.1.3.1.1.3 Impact on daily living and quality of life

In a survey of 1,286 patients from eight countries including the UK, the most common moderate/major impacts of PsA were on physical activity (78%), ability to perform certain activities (76%), work productivity (62%), and career path (57%) (129). A high proportion of patients reported a moderate/major impact on emotional/mental wellbeing (69%), romantic relationships/intimacy (56%), and relationships with family/friends (44%).

In a quantitative study of adult patients formally diagnosed with PsA and receiving treatment, which aimed to further understand the impact of PsA on patients' lives, PsA symptoms were reported to negatively affect completing daily activities, with patients agreeing they struggled or often could not perform activities related to (122):

- **Dressing:** do up buttons (78%), tie shoelaces (75%), put on socks (73%), squeeze shampoo bottles/open moisturiser tubs (72%)
- **Cooking and eating:** open jars/cartons/bottles (83%), open canned foods (76%), hold and use cutlery (60%), hold a glass or a mug (56%)
- **Work and hobbies:** sit at a desk for long periods (81%), play a musical instrument (73%), type on a keyboard (65%), and use a mobile phone (53%)
- **Simple household chores:** reach for items on the top or bottom shelf at the supermarket (76%), iron (70%), and turn a tap on (57%)
- **Transport**: drive a car (64%), take public transport (64%)
- **Caregiving**: care for children/dependents (72%).

In addition, the study found that PsA can have a negative impact on developing and maintaining relationships with loved ones; 53% of patients agreed strongly/slightly that their loved ones don't understand enough about PsA, 43% that their condition has created problems or arguments with their partner or close family members, 38% that their condition has prevented them/delayed them finding a life partner, and 31% that they have had a relationship end because their friends, spouse or significant other did not understand their condition. Patients with PsA may also struggle to make or keep friends; 60% of patients agreed strongly/slightly that they try to hide their condition from other people, 58% that their social life is limited because of their PsA, 54% are afraid of going near other people who might be ill due to their weak immune system caused by their PsA treatment, and 36% struggle to make and keep friends because of their PsA. Finally PsA has a negative impact on patient's career aspirations, and almost two fifths have felt discriminated against at work.

Patients with PsA also experience worse sleep quality vs those without PsA (130). Sleep quality among patients with PsA has been shown to deteriorate according to the severity of pain caused by skin lesions or joint involvement, and with the number of tender joints, and increased CRP (130). The decrease in quality of sleep is related to the intensity of fatigue (130), another common symptom of chronic inflammatory diseases of the joints and skin. Studies have reported severe fatigue is observed in ~30% of patients with PsA (17, 18). Using a numeric rating scale for fatigue (range 0–10), multiple factors were reported to contribute to fatigue (score >5/10) in PsA, including disease-related factors (current PSO, tender joint count [TJC], and enthesitis) and patient-related variables (years of education, female gender) (131). Higher fatigue scores (measured by Psoriatic arthritis Impact of Disease [PsAID]-12) in patients with PsA are also associated with significantly poorer HRQoL assessed by EQ-5D ($p<0.01$) (24).

In addition to fatigue, other symptoms of PsA contributing to reduced HRQoL include joint disease, pain, and skin disease (21-24). In the Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) study (conducted in Europe and North America), the most important factors for self-perceived disease severity were joint pain or swelling (45%), itching (18%), location and size of skin lesions (10%), and lack of sleep (7%) (21). In the US-based DISCONNECT study, both patients and physicians reported the most bothersome symptoms of PsA are joint pain, soreness, and tenderness (22). Another study showed that the severity of joint, and impact of skin symptoms are strongly associated with lower QoL (both $p<0.0001$, as measured by PsAQoL) (23).

The effect of PsA on patient QoL, with the disease impacting both physical and mental health aspects, can already be seen early in the course of the disease. Patients with early PsA (defined as first manifestation of arthritis, enthesitis, dactylitis, or spondyloarthritis less than two years before the first visit to the rheumatology clinic (29)) have significantly lower scores in all SF-36 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and component summaries (mental, and physical) compared with a matched, age adjusted general population ($p<0.05$ for all domains), demonstrating the negative impact of disease across both physical and mental health begins early after disease onset (30). At 5-years follow-up, HRQoL for patients with PsA remained significantly impaired compared with the general population, as indicated by lower scores in all SF-36 domains. Furthermore, patients with polyarthritis (≥5 peripheral joints) experienced poorer QoL in most SF-36 domains at inclusion, and at 5-years follow-up, vs patients with mono- or oligo-arthritis (<5 joints) (30), again highlighting the importance of rapid intervention and prevention of disease progression. Furthermore, a real-world point in time survey investigating the prescribing choices of first- or second-line TNFi vs non TNFi biologic therapy on PROs in

patients with PsA found that the use of non-TNFi biologics (IL-23i or IL-17i) as first-line therapy may results in improvements in PROs vs use of TNFi (132).

B.1.3.1.2 Epidemiology

The overall prevalence of diagnosed PsA in the UK is 0.19% (based on a cross-sectional study of 4,785,619 adult patients [aged 18 to 90 years] between 1994 and 2010 in The Health Improvement Network [THIN] database in the UK (3)). PsA commonly affects working age adults; most UK patients (67.7%) received their first read code for PsA between the ages of 30 and 60 years (median age: 44.8 years) (3). The prevalence peaked between 50–59 years (0.36%). Using the 2021 mid-year resident population estimate for the UK from the Office for National Statistics (ONS; 67,026,300 people), based on a prevalence of 0.19%, PsA is estimated to affect ~127,350 people (133). This is a conservative estimate, as the THIN study only included patients seeking medical intervention. PsA affects men and women equally (134), and up to 41% of people with the inflammatory skin condition PSO (10-12).

B.1.3.2 Economic burden

A significant economic burden is placed on the healthcare system by PsA. The total mean annual per patient healthcare cost of PsA in the UK is estimated to be £3,870 (standard error [SE]: £394), including medication costs, tests, accident and emergency visits, primary and secondary care consultations, and admitted care (31). Excluding medication costs, the total mean annual cost per patient is £1,586 (SD: £1,639). Increased functional impairment correlates with increased costs; each 1-point increase in Health Assessment Questionnaire – Disability Index (HAQ-DI) score (a measure of functional impairment) is associated with an increase of £547 in total annual healthcare costs (excluding medication costs; using 2012/2013, and 2014/2015 National Health Service [NHS] reference costs datasets for hospital episodes) (31). This relationship is mainly driven by the cost of secondary care consultations, but also admitted care and primary care consultations (31). Higher cost increases are associated with a HAQ-DI score of 2–3, and disease duration >10 years (31).

While the burden of PsA to the NHS is substantial, PsA also presents a significant burden to society and to patients. The indirect costs of PsA present a significant socioeconomic burden, resulting from absenteeism (sick leave, unemployment, leaving work before retirement age), and presenteeism (an individual is present at work but productivity is lower due to disease) (135). In a UK-based study (N=400), 26% of working-age patients with PsA were unemployed (136). In employed patients, absenteeism (14%), presenteeism (39%), and productivity loss (46%) reduced contributions at work, with higher disease activity associated with worse work outcomes (136). In another survey, 31.5% of patients reported missing work in the past 12 months as a result of their PsA, with 31.6% reporting an impact on their ability to work full time (21).

Another SLR of studies investigating the costs, benefits and burden of PsA reported that, despite differences in study design, definition of costs, and time periods making comparison difficult, the included studies agree that PsA is associated with 'enormous healthcare expenditure' including direct costs, and indirect costs that are mainly related to productivity losses (137). These direct and indirect costs of PsA were reported to be substantially higher vs patients with PSO without arthritis, or other inflammatory diseases, likely due to the presence of more than one complex condition (i.e. PSO and PsA) (137).

B.1.3.3 Clinical pathway of care and proposed positioning of bimekizumab

The aim of treatments for PsA is to improve the signs and symptoms of disease (including skin and nail involvement), inhibit the structural progression of joint damage, improve functional capacity and QoL, and reduce pain (33). Achieving higher treatment targets, such as MDA, Psoriasis Area and Severity Index (PASI)100, American College of Rheumatology (ACR)50 or ACR70 result in a greater improvement in patients' HRQoL (36, 37). Patients achieving MDA have significantly lower Psoriatic Arthritis Impact of Disease PsAID-12 scores than those who do not achieve MDA ($p<0.0001$), with all individual components less than 4 (considered a good outcome) in patients with MDA (36). In patients achieving higher PASI and ACR response categories, incremental benefits in QoL were observed (37).

Treatments for PsA include cDMARDs, bDMARDs, and tsDMARDs (32). The latest BSR guidelines recommend that b/tsDMARDs should be considered after failure or intolerance to one cDMARD in patients with active peripheral PsA (defined as at least three tender, and three swollen joints, or those with fewer joints but severe disease impact [defined as two or more domains involved], extra-articular involvement or impaired QoL), active psoriatic enthesitis, or active psoriatic dactylitis (35).

Currently, NICE guidance for patients with PsA with peripheral arthritis with three or more tender joints and three or more swollen joints do not recommend the use of b/tsDMARDs after one cDMARD (35). NICE guidance recommends that bDMARDs may be used to treat PsA after two cDMARDs have been tried (individually, or concurrently) (32). The current UK clinical pathway of care, based on NICE technology appraisal guidance (Figure 1) shows current recommended therapies for different populations of patients with PsA, including patients whose disease is poorly controlled after two or more cDMARDs (biologic-naïve), patients for whom a TNFi is contraindicated but would otherwise be considered (TNFi-CI), and patients who have had two or more cDMARDs and at least one bDMARD (biologic-experienced). Although several therapies are recommended for these patients, there remains an unmet need for novel therapies that

provide an additional therapeutic option for patients with this chronic, progressive, life-long condition (Section B.1.4).

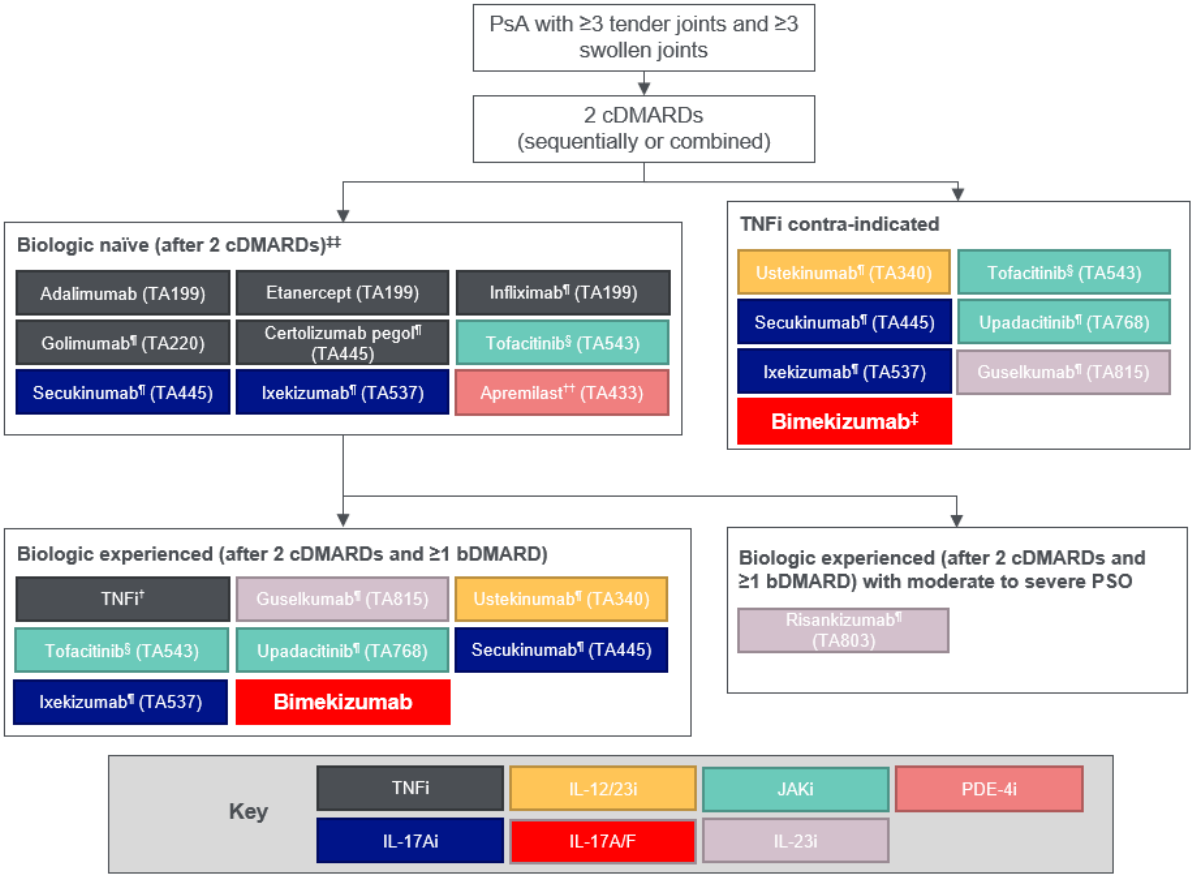
Bimekizumab is the first biologic designed to selectively inhibit both IL-17A and IL-17F (70), cytokines with overlapping biology that are independent pivotal drivers of inflammation and pathological bone formation in PsA (71-74). Bimekizumab is anticipated to be used in clinical practice (Figure 1), alone or in combination with MTX, for adult patients with active PsA 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
    - They have had two cDMARD and at least one bDMARD, or
    - 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 PsA (75)).

The most relevant comparator for this submission is the IL-17Ai, ixekizumab (see Table 1 in Section B.1.1 for justification).

Of note, bimekizumab, ixekizumab, and other therapies in the PsA clinical pathway of care (excluding JAKis) are also recommended by NICE for the treatment of patients with moderate to severe PSO (82, 138-146); these patients may have concomitant PsA (PsA affects up to 41% of people with PSO (of any severity) (10-12)).

Figure 1: The clinical pathway of care comprising current NICE recommended therapies and proposed positioning of bimekizumab



Sources: NICE NG65 (32); NICE TA199 (75); NICE TA220 (147); NICE TA445 (148); NICE TA543 (149); NICE TA537 (77); NICE TA433 (150); NICE TA340 (151); NICE TA768 (78); NICE TA815 (79); NICE TA803 (152).
†Includes all TNFi recommended for biologic naïve patients; ‡The proposed positioning for bimekizumab also includes patients who are intolerant to TNFi; ¶Alone or with MTX. The positioning for guselkumab, upadacitinib, and risankizumab also includes patients who are intolerant to DMARDs; §With MTX; ††Alone or with cDMARDs; ‡‡Due to the recent availability of TNFi biosimilars as first-line therapies after non-response to adequate trials of at least two cDMARDs, non-biosimilars are not expected to be used at first-line for the majority of patients, except for those for whom TNFi are contraindicated.
Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; i, inhibitor; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; NICE, National Institute for Health and Care Excellence; PDE-4, phosphodiesterase-4; PsA, psoriatic arthritis; PSO, psoriasis; TNF, tumour necrosis factor alpha.

B.1.4 Unmet need

Several unmet needs exist in the treatment of PsA (Section B.1.4.1.1 to Section B.1.4.1.4). Bimekizumab helps to address some of these unmet needs, providing patients with PsA who are b/tsDMARD-experienced or b/tsDMARD-naïve an additional, well-tolerated therapeutic option with a rapid and sustained response (Section B.3).

B.1.4.1.1 More treatment options that optimally treat joint and skin manifestations associated with PsA

Patients with PsA experience different manifestations, with current treatments achieving different levels of effectiveness on each (35). Clinical guidelines include treatment recommendations for manifestations such as peripheral arthritis, axial disease, enthesitis, dactylitis, and other non-articular manifestations (34, 35). The other non-articular manifestations are divided into the domains of PSO, uveitis, and IBD in the BSR 2022 guidelines (35), and skin PSO, and nail PSO in the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2021 guidelines (34). The guidelines recommend that, where possible, treatment should be selected to address all active domains of disease with the goal to achieve the lowest level of disease activity in all domains (34, 35).

Patients with PsA with more severe PSO have worse disease burden (i.e. pain, fatigue) and impaired QoL, with this psychosocial impairment maintained in those patients who achieve low disease activity (Disease Activity Index in PsA-Low Disease Activity [DAPSA-LDA]) with active PSO (25, 153, 154). This demonstrates the importance of skin symptoms on overall disease burden and the need to achieve optimal control of both domains. While a study has shown that improvement in joint symptoms alone is a larger driver for increasing patients HRQoL than improvement in skin symptoms alone, improvements in both joint and skin symptoms are required to achieve optimal patient HRQoL levels (155).

Several treatments are available for PsA (Figure 1), however, there is a lack of treatments able to adequately treat both joint and skin manifestations in both bDMARD-experienced, and TNFi-naïve populations. Data at Week 24 from clinical studies shows that over 50% of TNFi-experienced patients (38-47), and over 50% of bDMARD-naïve patients (38-40, 44, 46-54) treated with current advanced therapies fail to achieve ACR50, PASI90, or PASI100.

There is therefore a need for new treatment options that optimally treat both joint and skin manifestations associated with PsA in b/tsDMARD-experienced and b/tsDMARD-naïve patients.

B.1.4.1.2 Ability to achieve complete disease control or remission

Notably, according to two discrete choice experiment studies, including one UK-based study, efficacy is the attribute most frequently reported as most important by patients with PsA (156, 157).

Guidelines in PsA recommend a treat-to-target approach (including the recently published BSR PsA guidelines), aiming for low disease activity or remission (34, 35, 90). The composite outcome measures MDA, and very low disease activity (VLDA; which consider joints, and skin symptoms, pain, patient assessment of disease activity, enthesitis, and QoL) define a low

disease activity state or remission, respectively (see Appendix K for further details). The use of MDA is anticipated to grow, as guidelines recommend aiming for low disease activity (158, 159). However, even with currently available advanced therapies (bDMARDs and tsDMARDs), a substantial proportion of patients with PsA fail to achieve complete disease control or remission.

An SLR and meta-analysis investigating the prevalence of MDA in 12,469 patients with PsA treated with at least one biologic therapy across randomised controlled trials (RCTs; 2009–2017) and 45 real-world studies reported that the overall prevalence of MDA in real-world studies was only 37% (95% confidence interval [CI]: 34%, 41%) (160). Across the identified RCTs, at ~6 months follow-up, the proportion of patients achieving MDA when all bDMARDs were grouped (TNFi, IL-17i, and IL-12/23i) was 32% (95% CI: 27, 38), with a similar prevalence across the various modes of action (TNFi: 30% [95% CI: 27, 51]; IL-17i: 29% [95% CI: 23, 36]; IL-12/23: 23% [95% CI: 16, 32]) (160). Another SLR of real-world evidence reported that among studies using PsA-specific metrics, 35–85% of patients with PsA do not achieve MDA or low disease activity (LDA) (62).

Uncontrolled disease can result in irreversible joint damage and functional impairment (61). Achieving MDA, which corresponds to a state of low disease activity, leads to better radiographic outcomes (161, 162), and improved PROs (including QoL, functional ability, and work productivity) (163, 164). The rapid attainment of MDA is key for a positive impact on the lives of patients with PsA, as failure to achieve MDA in the first year after diagnosis has been associated with worse PROs, which persisted long-term (165).

This suggests that there is an unmet need for therapies with increased efficacy, which better help patients achieve low disease activity or remission and further optimise care for patients with PsA.

Furthermore, the achievement of LDA, as defined by other outcome measures such as DAPSA disease states and ACR50 criteria, has been associated with improved patient productivity, and fewer days affected by absenteeism and presenteeism in the household and workplace (166). As indirect costs such as absenteeism and presenteeism are significant contributors to the economic burden of PsA (135), more therapeutic options that help patients to achieve stringent disease outcomes may help ameliorate this socioeconomic burden.

B.1.4.1.3 A treatment with prolonged efficacy, and additional treatment options for patients who have failed previous therapy

In addition to increased efficacy, there is also an unmet need for additional therapeutic options that help patients to achieve their treatment goals, particularly as PsA is a lifelong disease (age of onset between 30 and 60 years in the UK (3)). Switching between b/tsDMARDs during long-term disease management is a recommended strategy for patients who do not experience a

benefit to or are intolerant of one treatment (35, 90). NICE technology appraisal (TA) guidance for available biologics suggests switching therapy if no response is observed at 12 weeks (e.g. TNFi) (75, 147, 167) to 16 weeks (e.g. IL-17Ai) (77, 148). The need for switching in patients who fail to respond adequately to, or are intolerant of a bDMARD is also acknowledged by the European Alliance of Associations for Rheumatology (EULAR), who recommend switching to another bDMARD or tsDMARD, including one switch within a class (90).

In clinical practice, switching from TNFi therapy occurs frequently. In a study of 141 UK patients with PsA, at the end of the study period (mean: 4.5 years [range: 3.4–5.5 years]), 56%, 15%, 5%, and 3% of patients remained on their first-, second-, third-, and fourth- or later line TNFi, respectively, while 21% permanently discontinued TNFi therapy (168). The mean duration of therapy for patients who remained on their initial TNFi therapy was 53.6 months (standard deviation [SD]: 6.6), and 19.2 months (SD: 16.6) in those who discontinued their first TNFi (9.7% discontinued within 3 months) (168). At subsequent therapy lines, the average duration of treatment with TNFi decreased, and the proportion of patients discontinuing treatment within 3 months of initiation increased, and successive switches of TNFi therapy were associated with progressively less benefit (168).

Several studies have reported that patients switching to a second TNFi have significantly poorer response and/or measures of disease activity compared with non-switch patients (63-65). In addition, an SLR of RCTs investigating IL-17Ai and IL-12/23i for patients who were intolerant to or have responded inadequately to TNFi therapy reported that although these therapies are still efficacious in these patients, their efficacy is attenuated compared with TNFi-naïve patients (66). The efficacy of ixekizumab, and secukinumab was significantly reduced in TNFi-experienced patients versus TNFi-naïve patients for the measures of ACR20 (risk ratio [RR]: 0.71 [95% CI: 0.62, 0.80]; p<0.001), ACR50 (RR: 0.55 [95% CI: 0.45, 0.66]; p<0.001), ACR70 (RR: 0.63 [95% CI: 0.47, 0.83]; p=0.001), and resolution of enthesitis (RR: 0.72 [95% CI: 0.61, 0.84]; p<0.001), and numerically lower for PASI75 (RR: 0.89 [95% CI: 0.73, 1.07]), PASI90 (RR: 0.79 [95% CI: 0.59, 1.05]), and resolution of dactylitis (RR: 0.88 [95% CI: 0.70, 1.10]). Another study found that approximately 40% of patients persisted on biologic therapy after 20 months of treatment, however only 20% of patients remained on any particular biologic after 5 years (169).

Clinicians in a UK advisory board indicated that patients who are poorly controlled after being on all available treatment classes may need to cycle back to previous therapies (80). There is therefore an unmet need for other therapeutic options that provide a sustained response. There is also a need for therapies that are effective in patients who need to switch from biologics (e.g. TNFi) due to lack of efficacy or intolerance, and in patients who are b/tsDMARD-naïve.

B.1.4.1.4 Improved patient treatment satisfaction and QoL

Among patients with PsA, 40–60% report moderate to severe disease while being treated with advanced therapies, including biologics (67). Poor treatment response in PsA is associated with a substantial negative impact on patients (68). A study of 3,714 patients with PsA receiving immunomodulatory therapy determined patients to be failing therapy if after ≥3 months physician-rated disease severity had worsened, remained severe, was unstable/deteriorating, or they were dissatisfied with disease control and/or did not consider treatment a success. These patients had significantly poorer HRQoL compared with those who had treatment success (as measured by EQ-5D-3L, SF-36 Physical Component Summary [PCS], Mental Component Summary [MCS]; $p<0.0001$ for all measures) (68). In addition, these patients reported significant impairments in physical functioning (according to HAQ-DI), activity, and work productivity ($p<0.0001$ for all measures) (68). A study investigating the impact of clinical features on PROs and treatment satisfaction in PsA highlighted that effective symptom management is key for improving patient HRQoL (170). Individual manifestations of PsA, including tender joints, enthesitis, fatigue, had significant impacts on patient HRQoL, daily activity, and treatment satisfaction in both patients and physicians (170). In another study of 3,426 patients self-reporting with PsA from North America and Europe, 90% expressed that they were unhappy with current treatment options, with a need for better therapies (21).

In a quantitative study of patients with PsA, 63% of patients would prefer a treatment that slowly alleviates all symptoms, rather than quick relief of just some (122).

B.1.5 Equality considerations

No equality issues are expected.

B.2 Key drivers of the cost effectiveness of the comparator(s)

Previous appraisals for the treatment of active PsA after inadequate response to cDMARDs have generally been aligned on their approach to efficacy outcomes, adverse events (AEs), treatment discontinuation, and costs

- Ten previous National Institute for Health and Care Excellence (NICE) appraisals have been published for the treatment of active PsA after inadequate response to cDMARDs (75, 77-79, 147-152, 171)
  - The most recent, technology appraisal (TA) 803, used a cost-comparison model to demonstrate cost savings, whereas the other nine TAs used a cost-utility model to demonstrate cost-effectiveness
- Key clinical efficacy outcomes used in previous analyses were Psoriatic Arthritis Response Criteria (PsARC) response, ACR20/50/70, PASI50/75/90/100, and Health Assessment Questionnaire-Disability Index (HAQ-DI) conditional on PsARC response
  - In TA445 (148), and TA815 the committee concluded these outcomes were appropriate (79)
- Consensus across all previous TAs is that patients who do not achieve a PsARC response at the time of response assessment should be withdrawn from treatment (75, 77-79, 147-152, 171)
- Resource use and associated costs considered in all previous TAs were drug acquisition costs, administration costs, monitoring costs, and AE costs. All previous TAs excluded AEs from the final analyses, with disutilities and costs associated with AEs for the intervention assumed to be equivalent to comparators (75, 77-79, 147-152, 171)

B.2.1 Clinical outcomes and measures

B.2.1.1 Overview of technology appraisals for PsA

In total, NICE have published guidance following ten technology appraisals for advanced treatments (with six different mechanisms of action: TNFi, IL-12/23i, IL-23i, IL-17Ai, JAKi, PDE-4i) in active PsA with inadequate response to cDMARDs (75, 77-79, 147-152, 171). The comparator for bimekizumab in this cost comparison submission is the IL-17Ai, ixekizumab, which was evaluated through the single technology appraisal (STA) process under NICE TA537 (77), with guidance published in August 2018.

Nine further guidance documents have been published for the treatment of PsA:

- Etanercept, infliximab, and adalimumab, evaluated in TA199 (75), published in August 2010 (multiple technology appraisal [MTA])
- Golimumab, evaluated in TA220 (147), published in April 2011 (STA)
- Ustekinumab, evaluated in TA340 (151), published in June 2015 (STA)
- Apremilast, evaluated in TA433 (150), published in February 2017 (STA)
- Certolizumab pegol, and secukinumab (148), evaluated in TA445, published in May 2017 (MTA)
- Tofacitinib, evaluated in TA543 (149), published in October 2018 (STA)
- Guselkumab, evaluated in TA711 (171), published in June 2021 (STA); guidance updated and replaced by TA815 (79) in August 2022
- Upadacitinib, evaluated in TA768 (78), published in February 2022 (STA)
- Risankizumab, evaluated in TA803 (152), published in July 2022 (fast track appraisal [FTA] cost comparison [CC]).

B.2.1.2 Key clinical effectiveness outcomes

In these appraisals, the key clinical efficacy outcomes used in the cost-effectiveness/cost-comparison analyses were:

- ACR20/50/70
- Psoriatic Arthritis Response Criteria (PsARC) response
- PASI50/75/90/100
- HAQ-DI conditional on PsARC response.

In TA445, the committee concluded that these outcomes were appropriate for the analysis, this conclusion was also reached by the committee in the most recent appraisal, TA815 (79, 167). A summary of committee comments and uncertainties surrounding these outcomes is presented in Table 3.

Table 3: Key clinical efficacy outcomes appraised in published NICE guidance for the treatment of PsA

Drug(s)/ appraisal	Outcomes	Manufacturer approach/assumptions	Committee comments
Etanercept, infliximab, and adalimumab TA199 (75)	• ACR • PsARC • PASI • HAQ-DI	• PsARC response used to model patients as responders/non-responders at a given time • The assessment group assumed that HAQ-DI score improves for patients that are on treatment within the initial 3-month trial period even if PsARC threshold was not reached; initial improvement was maintained for people continuing on TNFi • The assessment group assumed that patients who had a PASI75 response would gain at least 75% improvement in psoriasis compared with baseline PASI • The assessment group model derived the utility formula from PASI and HAQ	• The Committee considered that the recommendations to discontinue treatment based on an inadequate PsARC response at 12 weeks were valid • The committee agreed that it was reasonable to assume that the model was more sensitive to HAQ-DI score than PASI response signalling, and that the utility benefit was driven more by response in joint symptoms than skin disease
Golimumab TA220 (147)	• ACR • PsARC • PASI • HAQ-DI	The approach taken was consistent with previous submissions	The committee agreed that it was reasonable to assume that the model was more sensitive to HAQ-DI score than PASI response
Ustekinumab TA340 (151)	• ACR • PsARC • PASI • HAQ-DI	Patients gained a fixed improvement in HAQ-DI PASI score if a PsARC/PASI response was achieved	• The approach taken was consistent with previous submissions • The model was more sensitive to HAQ-DI score and PsARC response than PASI response • There was uncertainty surrounding the assumption that people have a fixed improvement in HAQ-DI score that is maintained during treatment, considering there was a differing MoA for the intervention, although the committee considered that the assumptions were generally sufficient for decision making
Apremilast TA433 (150)	• ACR • PsARC • PASI • HAQ-DI	PsARC responders retain their HAQ-DI score; HAQ-DI progression was explored in revised analyses	• The approach taken was consistent with previous submissions • There was uncertainty surrounding HAQ-DI assumptions considering there was a differing MoA for the intervention

Drug(s)/ appraisal	Outcomes	Manufacturer approach/assumptions	Committee comments
			• PsARC response was measured over a longer time period for the intervention; this could have strengthened cost-effectiveness
Certolizumab pegol, and secukinumab TA445 (148)	• ACR • PsARC • PASI • HAQ-DI	The approach taken was largely consistent with previous submissions; response was defined at 12 weeks by PsARC and PASI75 in the secukinumab model and at 24 weeks by PsARC in the certolizumab pegol model	The approach taken was consistent with previous submissions
Ixekizumab TA537 (77)	• ACR • PsARC • PASI • HAQ-DI	The approach was consistent with previous submissions (model based on TA445 (167))	The approach was consistent with previous submissions
Tofacitinib TA543 (149)	• ACR • PsARC • PASI • HAQ-DI	The approach taken was consistent with previous submissions; HAQ-DI scores remain constant when on treatment and progress in line with BSC when off treatment	The approach taken was consistent with previous submissions
Upadacitinib TA768 (78)	• ACR • PsARC • PASI • HAQ-DI	Following discontinuation, HAQ-DI scores rebound to a value between baseline and the value for non-responders; they then converge to non-responders' natural history	HAQ-DI scores should rebound to natural history from baseline as described by the company initially
Risankizumab TA803 (152)	• ACR • PsARC • PASI • HAQ-DI	Comparable efficacy proved	Similar overall health benefits to the comparator
Guselkumab TA711 (171)/ TA815 (79)	• ACR • PsARC • PASI • HAQ-DI	The approach taken was consistent with previous submissions (model based on TA445 (167))	The approach taken was consistent with previous submissions

Abbreviations: ACR, American College of Rheumatology; BSC, best supportive care; HAQ-DI, Health Assessment Questionnaire-Disability Index; MoA, mechanism of action; PASI, Psoriasis Area Severity Index; PsARC, Psoriatic Arthritis Response Criteria; TA, technology appraisal; TNFi, tumour necrosis factor alpha inhibitor.

There is consistency across TAs regarding outcomes assessed and used in economic modelling. PsARC response has been used to model patients as responders and non-responders at a time consistent with response assessment in clinical practice and/or the SmPC for the intervention. HAQ-DI and PASI scores have been used to capture treatment effects measured through specific symptoms experienced by patients on- and off-treatment.

The TA for risankizumab (TA803) (88) differs from other appraisals as it adopts a cost-comparison modelling framework in which network meta-analysis (NMA) outcomes for PsARC, ACR, PASI, HAQ-DI, and adverse events (AEs) were used to demonstrate comparable efficacy and safety to the comparator treatment (guselkumab). The assumptions regarding efficacy in this appraisal remain consistent with those used in earlier appraisals such as TA199 (75) and TA445 (148).

All of the previously considered key clinical efficacy outcomes are included in the NMA for the current submission (Section B.3.9.4). NMA results for other outcomes including MDA, dactylitis resolution (according to the Leeds dactylitis index [LDI]), enthesitis resolution (according to the Leeds enthesitis index [LEI]), and pain visual analogue scale (VAS) are also presented in Section B.3.9.4. Results for very low disease activity (VLDA), SF-36 PCS, SF-36 MCS, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) are presented in Appendix D.

B.2.1.3 AEs and treatment discontinuation

Further clinical outcomes discussed during committee meetings in the relevant TAs include AEs and discontinuation. A summary of manufacturer assumptions and committee comments relating to AEs and discontinuation is presented in Table 4 and Table 5, respectively.

Table 4: AE outcomes appraised in published NICE guidance for the treatment of PsA

Drug(s)/ Appraisal	Manufacturer approach/assumptions	Committee comments
Etanercept, infliximab, and adalimumab TA199 (75)	AEs not modelled	AEs considered comparable across treatments
Golimumab TA220 (147)	AEs not modelled	Uncertainty surrounding long-term profile; although comparable overall
Ustekinumab TA340 (151)	AEs not modelled	No committee comments
Apremilast TA433 (150)	AEs not modelled	Acceptable AE profile
Certolizumab pegol, and secukinumab TA445 (148)	AEs not modelled	Acceptable AE profile
Ixekizumab TA537 (77)	AEs not modelled	Acceptable AE profile
Tofacitinib TA543 (149)	AEs not modelled	Acceptable AE profile
Upadacitinib TA768 (78)	AEs not modelled	Acceptable AE profile

Drug(s)/ Appraisal	Manufacturer approach/assumptions	Committee comments
Risankizumab TA803 (152)	AEs not modelled	Acceptable AE profile
Guselkumab TA711 (171)/ TA815 (79)	Serious AEs modelled	The committee agreed with the ERG that AEs should be removed from the economic model

Abbreviations: AE, adverse event; ERG, evidence review group; NICE, National Institute for Health and Care Excellence; PsA, psoriatic arthritis; TA, technology appraisal.

AEs have been excluded from final analyses in all previous TAs, with disutilities and costs associated with AEs for the intervention assumed to be equivalent to comparators. In TA815 (79), the manufacturer modelled serious AEs in the base case, however was asked by the evidence review group (ERG) to provide a further analysis excluding AEs. The committee's preferred analyses excluded AEs.

Table 5: Discontinuation rates appraised in published NICE guidance for the treatment of PsA

Appraisal	Manufacturer approach/assumptions	Committee comments
Etanercept, infliximab, and adalimumab TA199 (75)	• 17% per annum withdrawal rate; calculated within the first 3 months of trial data; assumed for the long-term in the base-case analysis • A sensitivity analysis using 16% York model rate had little impact on results • The HAQ-DI score rebounds to natural history after withdrawal from treatment	• Treatment should be discontinued in patients without PsARC response at 12 weeks • People whose disease has a PASI75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response
Golimumab TA220 (147)	16.5% per annum withdrawal rate due to treatment failure/AEs	Treatment should be discontinued in patients without PsARC response at 12 weeks
Ustekinumab TA340 (151)	16.5% per annum withdrawal rate due to treatment failure/AEs	• Trial discontinuation was lower, but acceptable for decision making • Treatment should be discontinued in patients without PsARC response at 24 weeks
Apremilast TA433 (150)	16.5% per annum withdrawal rate due to treatment failure/AEs	Treatment should be discontinued in patients without PsARC response at 16 weeks
Certolizumab pegol, and secukinumab TA445 (148)	• 16.5% per annum withdrawal rate due to treatment failure/AEs • The PASI and HAQ-DI scores rebound to baseline following withdrawal from treatment in the secukinumab model • The HAQ-DI score rebounds to a worse position than baseline in the certolizumab pegol model	Treatment should be discontinued in patients without PsARC response at 12 and 16 weeks for certolizumab pegol and secukinumab, respectively

Appraisal	Manufacturer approach/assumptions	Committee comments
Ixekizumab TA537 (77)	• Treatment should be discontinued in patients without PsARC response at 12 weeks in line with trial data • 16.5% per annum withdrawal rate due to treatment failure/AEs	Treatment should be discontinued in patients without PsARC response at 16 weeks in line with the SmPC
Tofacitinib TA543 (149)	12-week probability of withdrawal of 3.96% due to any cause is applied, based on TA199 (75)	Treatment should be discontinued in patients without PsARC response at 12 weeks
Upadacitinib TA768 (78)	16.5% per annum withdrawal rate due to treatment failure/AEs	Treatment should be discontinued in patients without PsARC response at 12 weeks
Risankizumab TA803 (152)	• Treatment should be discontinued in patients without PsARC response at 24 weeks • 16.5% per annum withdrawal rate due to treatment failure/AEs	Treatment should be assessed from 16 weeks and discontinued in patients without PsARC response at 24 weeks. When there is only partial response, PASI75 response should be considered by a dermatologist
Guselkumab TA711 (171)/ TA815 (79)	• Treatment specific discontinuation rates used • Treatment should be discontinued in patients without PsARC response at 24 weeks	• Treatment discontinuation in patients that didn't have a PsARC response at 24 weeks was considered appropriate in line with the SmPC, however assessment of response at 16 weeks was also considered appropriate in line with clinical opinion. When there is only partial response, PASI75 response should be considered by a dermatologist • 16.5% per annum withdrawal rate should be used

Abbreviations: AE, adverse event; HAQ-DI, Health Assessment Questionnaire-Disability Index; NICE, National Institute for Health and Care Excellence; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; SmPC, summary of product characteristics; TA, technology appraisal.

Consensus across previous TAs is that patients who do not achieve a PsARC response at a time consistent with response assessment in clinical practice and/or the SmPC for the intervention, should be withdrawn from treatment. Furthermore, treatment failure and AEs suggest the use of a treatment discontinuation rate of 16.5% per annum in this indication, following on from calculations made in the York model used in TA199 rather than trial data from each TA. In previous TAs, patients whose disease has a PASI75 response at the time of response assessment, but whose PsARC response does not justify continuation of treatment, have been considered for continuation of treatment on the basis of skin response by dermatologists.

B.2.2 Resource use assumptions

Resource use and associated costs considered in TAs listed in Section B.2.1 were:

- Drug acquisition costs
- Administration costs
- Monitoring costs
- AE costs.

As bimekizumab and ixekizumab are administered every 4 weeks (Q4W) by subcutaneous (SC) injection, and monitoring frequency and costs for both treatments are expected to be identical as equal discontinuation rates are assumed (Section B.4.2.1.1), drug acquisition is the only resource use cost relevant to this appraisal. AE costs have been excluded in alignment with previous TAs and consistent with a post-hoc comparison of treatment-emergent adverse events (TEAEs) between bimekizumab and the adalimumab reference arm, where similar rates are reported (Section B.3.10.1.1). This approach aligns with the risankizumab company submission (TA803 (88)), and was accepted by the committee in that appraisal.

B.3 Clinical effectiveness

The efficacy and safety of bimekizumab for the treatment of PsA has been assessed in a clinical development programme including two completed Phase 3 randomised controlled trials (RCT)

- BE COMPLETE in patients who have had an inadequate response or were intolerant to prior TNFi therapy (defined as TNFi-inadequate response [IR]) (172)
- BE OPTIMAL in patients who are bDMARD-naïve (55)
- These studies fed into the ongoing open-label extension study, BE VITAL, investigating the long-term safety and efficacy of bimekizumab over a period of 3 years

In BE COMPLETE and BE OPTIMAL, bimekizumab was superior to placebo in improving the signs and symptoms of PsA across a range of outcomes assessing different disease domains. Both trials met their primary endpoint, with bimekizumab 160 mg every 4 weeks (Q4W) demonstrating a superior joint response, as measured by ACR50, at Week 16 vs placebo

- BE COMPLETE: 43% vs 7%; odds ratio (OR): 11.1; p<0.001
- BE OPTIMAL: 44% vs 10%; OR: 7.1; p<0.001

Across both trials, bimekizumab also demonstrated statistically significant and clinically meaningful improvements vs placebo across other joint, and skin efficacy outcomes, composite measures assessing multiple disease domains, inhibition of structural

progression, periarticular disease manifestations, and HRQoL/physical function outcomes at Week 16

- Bimekizumab demonstrated a higher ACR70 responder rate (the most stringent ACR endpoint) (nominal p<0.001 in both trials)
- A higher proportion of patients achieved almost clear skin (measured by PASI90 [p<0.001 both trials]), with a high proportion of patients achieving complete skin clearance (PASI100; BE COMPLETE: 59%; BE OPTIMAL: 47.5%)
- Bimekizumab achieved a higher response in composite measures including MDA response (p<0.001 in both trials), VLDA, and ACR50+PASI100 (i.e. combined joint and skin response)
- The PsARC responder rate was higher with bimekizumab, indicating a reduction in disease activity (nominal p<0.001 in both trials)
- Patients had greater inhibition of structural progression of joint damage vs placebo (measured in BE OPTIMAL only) in both the population at high risk of structural progression (p=0.001), and in the overall population (p=0.001) (assessed by change from baseline in van der Heijdes modified Total Sharp Score [vdHmTSS], with a higher proportion of patients experiencing no radiographic joint damage progression (change from baseline in vdHmTSS ≤0.5%) vs placebo
- In a pooled population of patients from BE COMPLETE and BE OPTIMAL, greater improvements in periarticular disease manifestations (enthesitis or dactylitis) were observed among patients with enthesitis or dactylitis at baseline, respectively (p=0.008 and p=0.002, respectively)
- Bimekizumab also demonstrated an improvement in axial disease vs placebo, as indicated by a greater mean reduction from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score in both trials
- Patients had better physical function, as measured by SF-36 Physical Component Summary (PCS) scores and HAQ-DI (p<0.001 in both trials)

Improvements with bimekizumab were seen as early as Week 4, and were sustained long-term

- Improvements vs placebo in joint (ACR criteria), and skin (PASI criteria) measures, combined joint and skin response (ACR50+PASI100), MDA, PsARC, and axial disease (as measured by BASDAI), and HRQoL/physical function often occurred as early as the first assessment after one dose of bimekizumab (Week 2 or Week 4)
- Long-term data over 52 weeks in BE COMPLETE (from BE VITAL) and BE OPTIMAL shows that the response to bimekizumab treatment is sustained. Results from the completed Phase 2 studies, BE ACTIVE (173) and BE ACTIVE 2 (174) also show the

response to bimekizumab is sustained, with efficacy maintained over 3 years of treatment (174)

Treatment with bimekizumab is generally well tolerated in patients with active PsA, with no new or unexpected safety concerns or signals observed across the clinical development programme

- In BE COMPLETE, to Week 16, the proportion of patients with serious treatment-emergent adverse events (TEAEs) was low, occurring in five (2%) patients in the bimekizumab arm and no patients in the placebo arm. No serious TEAEs were considered to be related to bimekizumab by the investigator
- In BE OPTIMAL, to Week 52, serious TEAEs were reported for 46 (7%) patients receiving bimekizumab, and ten (7%) receiving adalimumab. The majority of serious TEAEs were assessed as not related to the investigational medicinal product (IMP) by the investigator, were considered recovering or resolved, and did not lead to study discontinuation

A network meta-analysis (NMA) showed that bimekizumab provided statistically superior or similar treatment effects vs ixekizumab across different disease domains in TNFi-experienced and TNFi-CI populations. Bimekizumab and ixekizumab demonstrated similar risk of serious adverse events (SAE), treatment discontinuation, and discontinuation due to AEs in a mixed patient population (TNFi-experienced, and b/tsDMARD-naive)

- In the absence of head-to-head data vs ixekizumab, an NMA was performed to assess the comparative relative efficacy and safety in populations of patients who are TNFi-experienced or TNFi-CI
- In TNFi-experienced patients, bimekizumab demonstrated statistically superior treatment effects vs ixekizumab for ACR20, PASI100, PsARC, and enthesitis resolution (according to the Leeds Enthesitis Index [LEI]), and similar treatment effects vs ixekizumab for ACR50, ACR70, PASI75, PASI90, MDA, dactylitis resolution (according to the Leeds Dactylitis Index [LDI]), HAQ-DI, and pain visual analogue scale (VAS)
- In TNFi-CI patients, bimekizumab demonstrated statistically superior treatment effects vs ixekizumab for ACR70, and PsARC, and similar treatment effects vs ixekizumab for ACR20, ACR50, PASI75, PASI90, and PASI100
- In a mixed population of patients (TNFi-experienced, or b/tsDMARD-naive), bimekizumab was similar to ixekizumab for SAEs, discontinuation, and discontinuation due to AEs. Notably, the safety NMAs were based on low numbers of events for bimekizumab, and ixekizumab

B.3.1 Identification and selection of relevant studies

An SLR was conducted to identify all relevant clinical evidence on the efficacy and safety of bimekizumab and other therapies for the treatment of patients with PsA. The SLR and subsequent SLR updates identified a total of 540 records reporting on 66 unique trials. Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are provided in Appendix D.

B.3.2 List of relevant clinical effectiveness evidence

An overview of the studies of bimekizumab for the treatment of active PsA that are relevant to this submission is provided in Table 6.

Table 6: Overview of relevant clinical evidence informing the submission

Study	Presentation in submission	Primary study reference(s)
Primary evidence		
BE COMPLETE (PA0011; NCT03896581)†	Data to Week 16 presented in Section B.3.6.1.1	Merola et al, 2023 (172) supplemented with data from the Week 16 CSR (175), CSR TFL data on file (176), and Sharma et al, 2023 (177)
BE OPTIMAL (PA0010; NCT03895203)†	Data to Week 52 presented in Section B.3.3.1.1.2	McInnes et al, 2023 (55) supplemented with data from the Week 52 CSR (178), Ritchlin et al, 2022 (179) and Week 52 CSR TFLs (180)
BE VITAL (PA0012; NCT04009499)	BE COMPLETE data from BE VITAL (Week 16–Week 52) presented in Section B.3.6.1.1.4	Data on file (181)
Supportive long-term efficacy and safety evidence		
BE ACTIVE (PA0008; NCT02969525)	Key outcomes presented in Section B.3.6.2.1	Ritchlin et al, 2020 (173) supplemented with data from the CSR (182) and TFLs (183)
BE ACTIVE 2 (PA0009; NCT03347110)	Key outcomes presented in Section B.3.6.2.1	Coates et al, 2022 (174) supplemented with data from the CSR (184) and TFLs (183)

†Patients in these studies fed into the OLE study BE VITAL.
Abbreviations: CSR, clinical study report; OLE, open-label extension; TFL, tables, figures, and listings.

The primary sources for the clinical effectiveness of bimekizumab for the treatment of PsA are the two completed Phase 3 RCTs, BE COMPLETE in patients who have had a previous inadequate response or intolerance to TNFi therapy for PsA or PSO (termed TNFi-IR]) (172), and BE OPTIMAL in patients who are bDMARD-naïve (55) (Table 7)[a]. BE VITAL is an ongoing, three-year open-label extension study of patients completing BE COMPLETE, and BE OPTIMAL, with Week 16–Week 52 data for BE COMPLETE from BE VITAL currently available (181). The

[a] Please see page 19 for a reminder of the population terminology.

completed Phase 2 studies BE ACTIVE (173) and BE ACTIVE 2 (174) provide supportive long-term efficacy and safety evidence up to 3 years for bimekizumab (Table 8).

A summary of endpoints commonly used in clinical studies in PsA is provided in Appendix K. These include joint measures (ACR20/50/70, PsARC), PSO-related outcomes (PASI75/90/100, modified Nail Psoriasis Severity Index [mNAPSI]), composite outcomes for example MDA, and VLDA, measures of structural progression (van der Heijde modified Total Sharp Score [vdHmTSS]), measures of enthesitis, and dactylitis resolution (LEI, LDI), functional capacity and HRQoL outcomes (HAQ-DI), and measures of axial disease (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]). The ability to measure disease activity in PsA is pivotal for the treat-to-target approach to care, which defines a distinct target such as minimal disease activity (MDA) (35).

B.3.2.1 Primary evidence

An overview of BE COMPLETE and BE OPTIMAL is provided in Table 7.

Table 7: BE COMPLETE and BE OPTIMAL: Overview of study design

Study	BE COMPLETE (PA0011) (175)	BE OPTIMAL (PA0010) (178)
Study design	A 16-week Phase 3, multicentre, randomised, double-blind, placebo-controlled trial	A 52-week Phase 3, multicentre, randomised, double-blind, placebo-controlled, active reference study comprising a 16-week double-blind placebo-controlled period, and a 36-week treatment blind period
Population	Adult patients (≥18 years) with a diagnosis of adult-onset, active PsA (based on CASPAR) and: • Disease duration ≥6 months • TJC ≥3 out of 68 and SJC ≥3 out of 66 • Negative for rheumatoid factor and anti-cyclic CCP antibodies • 1 active psoriatic lesions and/or a documented history of PSO	
	An inadequate response† or intolerance to treatment with one or two TNFi for either PsA or PSO	No current or prior exposure to biologics for the treatment of PsA or PSO
Intervention(s)	Bimekizumab 160 mg Q4W (administered as a SC injection using a 160 mg/mL pre-filled syringe)	
Comparator(s)	Placebo Q4W (0.9% sodium chloride aqueous solution administered as a SC injection using a 1 mL pre-filled syringe)	Placebo Q2W (0.9% sodium chloride aqueous solution administered as a SC injection using a 1 mL pre-filled syringe)
Reference arm (trial not statistically powered for comparison)	None	Adalimumab 40 mg Q2W (administered as a SC injection using a 40 mg/0.8 mL or 40 mg/0.4 mL pre-filled, single use syringe)
Indicate if study supports application for marketing authorisation	Yes	Yes
Reported outcomes specified in the decision problem	• Disease activity ○ ACR20 response at Week 16 ○ ACR50 response at Week 16 (primary endpoint) ○ ACR70 response at Week 16 ○ PASI75 response at Week 16 ○ PASI90 response at Week 16 ○ PASI100 response at Week 16 ○ Composite ACR50+PASI100 response at Week 16	• Disease activity ○ ACR20 response at Week 16 and Week 52 ○ ACR50 response at Week 16 (primary endpoint) and Week 52 ○ ACR70 response at Week 16 and Week 52 ○ PASI75 response at Week 16 and Week 52 ○ PASI90 response at Week 16 and Week 52 ○ PASI100 response at Week 16 and Week 52

Study	BE COMPLETE (PA0011) (175)	BE OPTIMAL (PA0010) (178)
	○ PsARC at Week 16 ○ MDA response at Week 16 ○ VLDA response at Week 16 ○ mNAPSI resolution at Week 16 • Functional capacity ○ HAQ-DI change from baseline at Week 16 • Axial outcomes ○ BASDAI change from baseline at Week 16 • Adverse effects of treatment ○ AEs, including deaths at Week 16 • HRQoL ○ SF-36 PCS change from baseline at Week 16	○ Composite ACR50+PASI100 response at Week 16 and Week 52 ○ PsARC at Week 16 and Week 52 ○ MDA response at Week 16 and Week 52 ○ VLDA response at Week 16 and Week 52 ○ mNAPSI resolution at Week 16 and Week 52 • Functional capacity ○ HAQ-DI change from baseline at Week 16 and Week 52 • Disease progression ○ vdHmTSS change from baseline at Week 16 ○ Proportion of patients with no radiographic progression (vdHmTSS change from baseline ≤0.5%) at Week 16 and Week 52 • Periarticular disease ○ Enthesitis resolution (LEI) at Week 16 (pooled population of BE COMPLETE, and BE OPTIMAL) ○ Dactylitis resolution (LDI) at Week 16 (pooled population of BE COMPLETE, and BE OPTIMAL) • Axial outcomes ○ BASDAI change from baseline at Week 16 and Week 52 • Adverse effects of treatment ○ AEs, including deaths at Week 16 and Week 52 • HRQoL ○ SF-36 PCS change from baseline at Week 16 and Week 52
All other reported outcomes	N/A	N/A

†Lack of efficacy after ≥3 months of therapy at an approved dose.
Abbreviations: ACR, American College of Rheumatology; AE, adverse event; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BSA, body surface area; CASPAR, Classification Criteria for Psoriatic Arthritis; CCP, cyclic citrullinated peptide; HAQ-DI, Health Assessment Questionnaire for Rheumatoid Arthritis-disability index; HRQoL, health-related quality of life; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; N/A, not applicable, MDA, minimal disease activity; mNAPSI, modified Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; PSO, psoriasis; QXW, every X weeks; SC, subcutaneous; SF-36 PCS, short form-36 Physical Component Summary; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitor; vdHmTSS, van der Heijde modified Total Sharp Score; VLDA, very low disease activity.

B.3.2.2 Supporting evidence

An overview of BE ACTIVE and BE ACTIVE 2 is provided in Table 8.

Table 8: BE ACTIVE and BE ACTIVE 2: Overview of study design

Study	BE ACTIVE (PA0008; NCT02969525) (173, 182)	BE ACTIVE 2 (PA0009; NCT03347110) (174)
Study design	Phase 2b, multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study	Multicentre, OLE study (duration up to 3 years)
Population	Adult patients (≥18 years) with a diagnosis of adult-onset, active PsA (based on CASPAR) and: • Disease duration ≥6 months • TJC ≥3 out of 78 and SJC ≥3 out of 76 • Negative for rheumatoid factor and anti-cyclic CCP antibodies • ≥1 active psoriatic lesions and/or a documented history of PSO • May be TNFi-naïve or may have received one prior TNFi and experienced an inadequate response to previous treatment given for ≥3 months, been intolerant to administration, or lost access to TNFi for other reasons	Patients who completed BE ACTIVE without meeting any withdrawal criteria
Intervention(s)	Bimekizumab in different dosing regimens (administered as two SC injections using a 160 mg/mL single use dose vial): • 16 mg Q4W (one 0.1 mL bimekizumab injection, one 0.1 mL placebo) • 160 mg Q4W (one 1.0 mL bimekizumab injection, one 1.0 mL placebo) • 320 mg Q4W (two 1.0 mL bimekizumab injections) • 320 mg LD (two 1.0 mL bimekizumab injections) followed by 160 mg (one 1.0 mL bimekizumab injection, one 1.0 mL placebo) starting at Week 4 and Q4W thereafter	Bimekizumab 160 mg Q4W (administered as one SC injection using a 1 mL pre-filled syringe)
Comparator(s)	Placebo Q4W (0.9% sodium chloride aqueous solution administered as 2 x 1mL injections)	–
Indicate if study supports application for marketing authorisation (yes/no)	Yes	Yes
Reported outcomes specified in the decision problem	• Disease activity ○ ACR20 to Week 152 ○ ACR50 to Week 152 ○ ACR70 to Week 152 ○ PASI75 at Week 12, 48 and 152 ○ PASI90 at Week 12, 48 and 152 ○ PASI100 at Week 12, 48 and 152	

Study	BE ACTIVE (PA0008; NCT02969525) (173, 182)	BE ACTIVE 2 (PA0009; NCT03347110) (174)
	○ MDA to Week 152 ○ VLDA to Week 152 ○ composite ACR50+PASI100 at Week 48, 96 and 152 ○ PsARC to Week 48, 96, and 152 • Functional capacity ○ HAQ-DI at Week 12, 48, 96, and 152 • Periarticular disease ○ Dactylitis resolution (LDI) to Week 152 ○ Enthesitis resolution (MASES) to Week 152 • Adverse effects of treatment ○ AEs, including deaths • HRQoL ○ SF-36 PCS at Week 12, 48, 96, and 152	
All other reported outcomes	• N/A	

Abbreviations: ACR, American College of Rheumatology; AE, adverse event; CASPAR, Classification Criteria for Psoriatic Arthritis; CCP, cyclic citrullinated peptide; HAQ-DI, Health Assessment Questionnaire-Disability Index; HRQoL, health-related quality of life; LD, loading dose; LDI, Leeds Dactylitis Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MDA, minimal disease activity; N/A, not applicable; OLE, open-label extension; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; PSO, psoriasis; Q4W; every 4 weeks; SC, subcutaneous; SF-36 PCS, short form-36 physical component summary; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor alpha inhibitor; VLDA, very low disease activity.

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Primary evidence

Primary evidence comes from two Phase 3 trials (BE COMPLETE, BE OPTIMAL). A combined summary of the trial designs is presented where possible.

B.3.3.1.1 Trial design

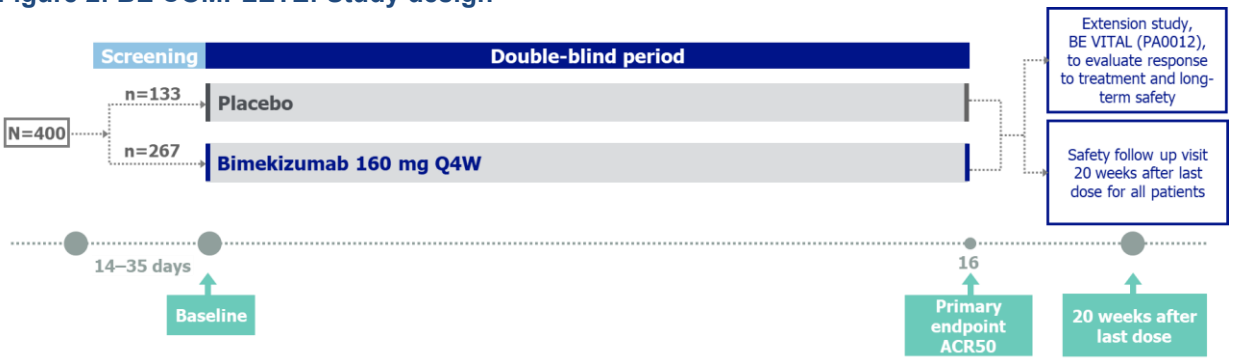
B.3.3.1.1.1 BE COMPLETE

BE COMPLETE is a Phase 3, multicentre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab in patients with active PsA who have had an inadequate response or were intolerant to prior TNFi therapy (TNFi-IR). Patients were randomised 2:1 to receive either bimekizumab 160 mg SC Q4W or placebo Q4W, and were stratified according to region and prior TNFi exposure (inadequate response to one or two prior TNFi or intolerance to TNFi).

The study included three periods: a screening period (≥14 days to ≤35 days), a double-blind treatment period (16 weeks), and a safety follow-up (SFU) period (20 weeks after the final dose of investigational medicinal product [IMP]) for all patients who did not enter the open label extension (OLE) study BE VITAL (Figure 2).

During the double-blind treatment period, visit windows of ±3 days (relative to the Day 1 baseline visit) were allowed from the first dose at all visits through to Week 16. Patients who discontinued the IMP during the double-blind treatment period returned for all scheduled visits through to Week 16, and for the SFU visit. Patients who withdrew from the study had an early termination visit and returned for a SFU visit 20 weeks after the final dose of IMP. The maximum study duration per patient was up to 37 weeks, and patients who completed Week 16 were eligible for enrolment in the OLE study BE VITAL.

Figure 2: BE COMPLETE: Study design



Abbreviations: ACR, American College of Rheumatology; Q4W, every 4 weeks.

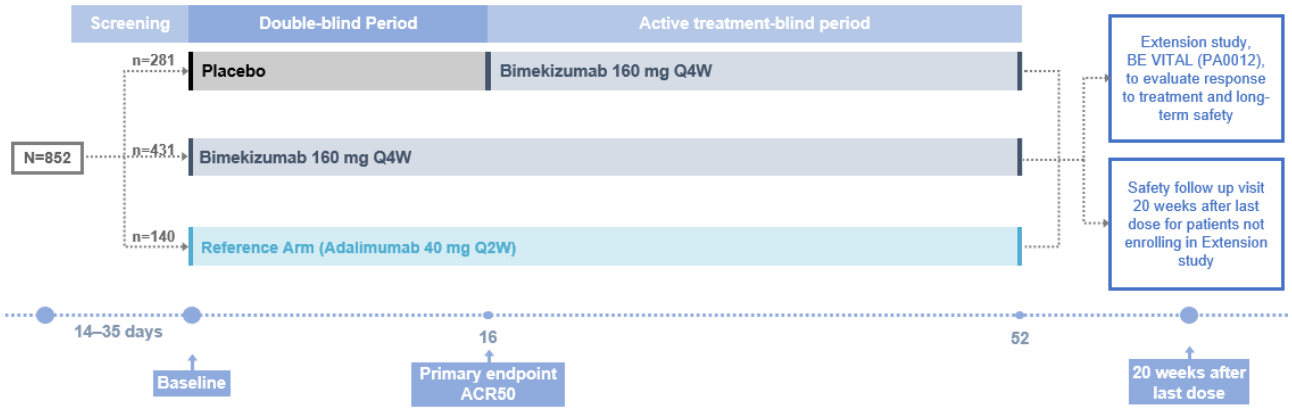
B.3.3.1.1.2 BE OPTIMAL

BE OPTIMAL is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, active-reference study evaluating the efficacy and safety of bimekizumab in patients with active PsA who are bDMARD-naïve. BE OPTIMAL included three periods: a screening period (≥14 days to ≤35 days), a treatment period (52 weeks), and a SFU period (20 weeks after the final dose of IMP) for patients who did not enter the OLE study (Figure 3). The maximum study duration was up to 73 weeks per patient.

The treatment period consisted of a 16-week double-blind treatment period followed by a 36-week active treatment-blind period. During the double-blind period, patients were randomised 3:2:1 (stratified by region, and bone erosion [0, ≥1]) to receive bimekizumab 160 mg SC Q4W, placebo SC every 2 weeks (Q2W), or active reference (adalimumab 40 mg SC Q2W). The adalimumab active reference arm was included to establish the long-term safety of bimekizumab and maintain blinding of the active treatment under investigation until Week 52. BE OPTIMAL was not designed to test superiority or non-inferiority of bimekizumab versus adalimumab. The lack of formal statistical comparisons between the intervention and reference arms is consistent with other pivotal PsA trials utilising a reference arm (49, 185). Visit windows of ±2 days (relative to the Day 1 baseline visit) were allowed for all visits through to Week 16. After Week 16, patients entered the active treatment-blind period; at the Week 16 visit, patients in the bimekizumab and adalimumab arms continued the same treatment as the double-blind period, while patients in the placebo arm were reallocated to the bimekizumab arm. After Week 16, visit windows of ±3 days were allowed for all visits.

Patients who completed the active treatment-blind period were given the opportunity to enter the OLE study BE VITAL. Patients not entering the OLE entered the 20-week SFU period. Patients who withdrew early from the study underwent an early termination visit assessment and entered the SFU Period. Patients who withdrew from IMP during the double-blind or active treatment-blind period were encouraged to return for all remaining scheduled visits up to Week 52 and the SFU visit.

Figure 3: BE OPTIMAL: Study design



†The adalimumab 40 mg Q2W treatment arm serves as an active reference. The study was not powered for statistical comparisons of adalimumab to bimekizumab or placebo.
Abbreviations: ACR, American College of Rheumatology; Q4W, every 4 weeks.

B.3.3.1.2 Overview of study methods

An overview of the study methods is provided in Table 9, with full details provided in Appendix J.

Table 9: BE COMPLETE and BE OPTIMAL: Summary of trial methodology

	BE COMPLETE	BE OPTIMAL
Settings and locations where data were collected	92 sites across: Australia, Canada, Czech Republic, Germany, Hungary, Italy, Japan, Poland, Russia, United Kingdom, United States (2 UK patients across 1 UK site)	135 sites across: Australia, Belgium, Canada, Czech Republic, France, Germany, Hungary, Italy, Japan, Poland, Russia, Spain, United Kingdom, United States (2 UK patients across 2 UK sites)

Key inclusion criteria (full details provided in Appendix J)	• ≥18 years of age
	• Documented diagnosis of adult-onset, active PsA:
	  ○ Meeting the CASPAR classification criteria for ≥6 months prior to screening
	  ○ Baseline TJC ≥3 out of 68 and SJC ≥3 out of 66 (dactylitis of a digit counts as 1 joint each)
	• Negative for rheumatoid factor and anti-CCP antibodies
	• ≥1 active psoriatic lesion(s) and/or a documented history of PSO	

	• History of inadequate response (lack of efficacy after ≥3 months of therapy at an approved dose) or intolerance to treatment with 1 or 2 TNFi for either PsA or PSO	• Patient considered by investigator to be a suitable candidate for treatment with adalimumab per regional labelling and had no contraindications to receive adalimumab as per the local label
Key exclusion criteria (full details provided in Appendix J))	• Current or prior exposure to any biologics except TNFi for the treatment of PsA or PSO, including participation in a bimekizumab clinical study (who received ≥1 dose of IMP, including placebo)	• Current or prior exposure to any biologics for the treatment of PsA or PSO, including participation in a bimekizumab clinical study (who received ≥1 dose of IMP, including placebo)
Method of study drug administration	• Bimekizumab 160 mg Q4W SC • Placebo Q4W SC	• Bimekizumab 160 mg Q4W SC (with a dummy/placebo injection Q4W on weeks

	BE COMPLETE	BE OPTIMAL
(full details provided in Appendix J)		the patient was not scheduled to receive bimekizumab to preserve blinding) • Placebo Q2W SC • Adalimumab (active reference) 40 mg Q2W
Permitted medication (full details provided in Appendix J)	Concomitant NSAIDs/COX2i, analgesic, oral corticosteroids, or cDMARDs at stable doses (subject to restrictions outlined in the inclusion and exclusion criteria of BE COMPLETE and BE OPTIMAL)	

Abbreviations: CASPAR, Classification Criteria for Psoriatic Arthritis; CCP, cyclic citrullinated peptide; COX-2i, cyclooxygenase-2 inhibitor; IMP, investigational medicinal product; NSAID, non-steroidal anti-inflammatory drug; PsA. Psoriatic arthritis; PSO, psoriasis; QXW, every x weeks; SC, subcutaneous; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor alpha inhibitor; UK, United Kingdom.

B.3.3.1.3 Outcomes specified in the scope

B.3.3.1.3.1 Primary endpoint

The primary endpoint in both BE COMPLETE and BE OPTIMAL was the ACR50 response at Week 16. In other RCTs investigating treatments for PsA, including the IL-17Ai ixekizumab (43, 49), the primary endpoint was ACR20 response. ACR50 was used because it is a more stringent measure of joint outcome, with patients needing to achieve a 50% or greater improvement relative to baseline, rather than 20% or greater, representing a more robust clinical response (186). In a TNFi-IR patient population from BE COMPLETE, and bDMARD-naïve population in BE OPTIMAL (pooled regardless of treatment arm in each study), patients achieving ACR50 demonstrated a greater mean reduction in pain (as assessed by Patient's Assessment of Arthritis Pain [PtAAP]), and greater mean improvements in physical function and HRQoL (as measured by EQ-5D-5L-VAS, EQ-5D-3L utility [UK tariff], SF-36 PCS, and HAQ-DI] at 16-weeks than those achieving ACR20 (187, 188).

B.3.3.1.3.2 Secondary endpoints

The secondary endpoints in BE COMPLETE and BE OPTIMAL relevant to the scope are provided in Table 10.

Table 10: BE COMPLETE and BE OPTIMAL: Secondary endpoints relevant to the scope

Endpoint	BE COMPLETE	BE OPTIMAL
Ranked secondary efficacy endpoints		
HAQ-DI CFB at Week 16	✓	✓
PASI90 response at Week 16 (patients with PSO involving ≥3% BSA at baseline)	✓	✓
SF-36 PCS CFB at Week 16	✓	✓
MDA response at Week 16	✓	✓
vdHmTSS CFB at Week 16 (patients with elevated hs-CRP and/or ≥1 bone erosion at baseline)	–	✓
Enthesitis-free state (based on LEI) at Week 16 (patients with enthesitis at baseline) in the pooled population of BE COMPLETE and BE OPTIMAL	–	✓
Dactylitis-free state (based on LDI) at Week 16 (patients with dactylitis at baseline) in the pooled population of BE COMPLETE and BE OPTIMAL	–	✓
vdHmTSS CFB at Week 16 (all patients)	–	✓
Non-ranked secondary efficacy endpoints		
PASI90 at Week 4 (patients with PSO involving ≥3% BSA at baseline)	✓	✓
ACR20 response at Week 16	✓	✓
ACR70 response at Week 16	✓	✓
Other efficacy endpoints		
ACR20, ACR50, ACR70 response by visit to Week 52 (BE OPTIMAL) or Week 16 (BE COMPLETE)	✓	✓
PASI75, PASI90 and PASI100 response in the subgroup of patients with PSO involving ≥3% BSA at baseline by visit to Week 52 (BE OPTIMAL) or Week 16 (BE COMPLETE)	✓	✓
Composite endpoint composed of ACR50+PASI100 response in patients with PSO involving ≥3% BSA at baseline by visit to Week 52 (BE OPTIMAL); at Week 16 (BE COMPLETE)	✓	✓
Proportion of PsARC responders by visit to Week 52 (BE OPTIMAL); at Week 16 (BE COMPLETE)	✓	✓
Proportion of ACR50 responders at Week 16 and maintaining response at Week 52	–	✓
MDA response by visit to Week 52 (BE OPTIMAL); at Week 16 (BE COMPLETE)	✓	✓
VLDA response by visit to Week 52 (BE OPTIMAL); at Week 16 (BE COMPLETE)	✓	✓
Proportion of patients with no radiographic joint damage progression (CFB in vdHmTSS of ≤0.5) at Week 16 and Week 52 (in all patients)	–	✓
CFB in BASDAI in the subgroup of patients with axial involvement defined by a score of ≥4 at baseline by visit to Week 52 (BE OPTIMAL) or to Week 16 (BE COMPLETE)	✓	✓
CFB in mNAPSI score in the subgroup of patients with nail PSO at baseline at Week 16 and Week 52 (BE OPTIMAL); at Week 16 (BE COMPLETE)	✓	✓

Abbreviations: ACR, American College of Rheumatology; BASDAI; Bath Ankylosing Spondylitis Disease Activity Index, BSA, body surface area; CFB, change from baseline; HAQ-DI, Health Assessment Questionnaire-Disability Index; hs-CRP, high sensitivity C-reactive protein; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; mNAPSI, modified Nail Psoriasis Severity Index; PASI, Psoriasis Area and

Severity Index; PsARC; psoriatic arthritis response criteria; PSO, psoriasis; SF-36 PCS, short form-36 physical component summary; vdHmTSS, Van der Heijde Modified Total Sharp Score; VLDA, very low disease activity.

B.3.3.1.4 Baseline patient characteristics

In BE COMPLETE, and BE OPTIMAL, patient baseline demographics were generally well balanced between the treatment groups (Table 11).

Overall, baseline disease characteristics of the study participants in both trials were reflective of a population of patients with active PsA (Table 11), and the bimekizumab and placebo treatment groups were generally well balanced with respect to PsA-related and other baseline disease characteristics (Table 11).

In BE COMPLETE, 77% of patients had an inadequate response to one TNFi, with the remaining patients having an inadequate response to two TNFi (11%), or intolerance to TNFi (12%). At baseline, 63% of patients in BE COMPLETE, and 79% of patients in BE OPTIMAL had received prior cDMARDs (Appendix J).

Table 11: BE COMPLETE and BE OPTIMAL: Baseline patient demographic and disease characteristics (RS)

Study	BE COMPLETE			BE OPTIMAL			
Variable	PBO N=133	BKZ Q4W N=267	Overall N=400	PBO N=281	BKZ Q4W N=431	ADA Q2W reference arm N=140	Overall N=852
Age (years)							
Mean (SD)	51.3 (12.9)	50.1 (12.4)	50.5 (12.5)	48.7 (11.7)	48.5 (12.6)	49.0 (12.8)	48.7 (12.3)
Gender, n (%)							
Male	60 (45)	130 (49)	190 (48)	127 (45)	201 (47)	71 (51)	399 (47)
BMI (kg/m^2)							
Mean (SD)	29.0 (5.4)	30.1 (6.5)	29.8 (6.2)	29.6 (6.1)	29.2 (6.8)	28.4 (5.9)	29.2 (6.4)
Racial group, n (%)							
White	128 (96.2)	256 (95.9)	384 (96.0)	270 (96.1)	410 (95.1)	133 (95.0)	813 (95.4)
Time since first diagnosis of PsA (years)							
n	132	266	398	279	423	139	841
Mean (SD)	9.2 (8.1)	9.6 (9.9)	9.5 (9.3)	5.6 (6.5)	6.0 (7.3)	6.1 (6.8)	5.9 (7.0)
BSA ≥3% affected by PSO							
n (%)	88 (66)	176 (66)	264 (66)	140 (50)	217 (50)	68 (49)	425 (50)
PASI score for patients with PSO involving ≥3% BSA at baseline							
Mean (SD)	8.5 (6.6)	10.1 (9.1)	9.6 (8.4)	7.9 (5.6)	8.2 (6.8)	8.5 (7.6)	8.1 (6.6)
BASDAI, n (%)							
<4	37 (28)	63 (24)	100 (25)	68 (24)	119 (28)	33 (24)	220 (26)
≥4	96 (72)	204 (76)	300 (75)	213 (76)	311 (72)	107 (76)	631 (74)
Missing	–	–	–	0	1 (0.2)	0	1 (<1)
TJC of 68 joints							
Mean (SD)	19.3 (14.2)	18.4 (13.5)	18.7 (13.8)	17.1 (12.5)	16.8 (11.8)	17.5 (13.1)	17.0 (12.2)
SJC of 66 joints							
Mean (SD)	10.3 (8.2)	9.7 (7.5)	9.9 (7.7)	9.5 (7.3)	9.0 (6.2)	9.6 (7.1)	9.2 (6.7)

Study	BE COMPLETE			BE OPTIMAL			
Variable	PBO N=133	BKZ Q4W N=267	Overall N=400	PBO N=281	BKZ Q4W N=431	ADA Q2W reference arm N=140	Overall N=852
hs-CRP ≥6 mg/L							
n, %	59 (44)	118 (44)	177 (44)	121 (43)	158 (37)	44 (31)	323 (38)
HAQ-DI							
Mean (SD)	1.04 (0.69)	0.97 (0.59)	0.99 (0.62)	0.89 (0.61)	0.82 (0.59)	0.86 (0.54)	0.85 (0.59)
Nail PSO, n (%)							
Yes	83 (62)	159 (60)	242 (61)	156 (56)	244 (57)	75 (54)	475 (56)
No	49 (37)	108 (40)	157 (39)	125 (45)	180 (42)	65 (46)	370 (43)
Missing	1 (1)	0	1 (<1)	0	7 (2)	0	7 (1)
Dactylitis (LDI), n (%)							
Yes†	14 (11)	34 (13)	48 (12)	33 (12)	56 (13)	11 (8)	100 (12)
No	118 (89)	233 (87)	351 (88)	248 (88)	368 (85)	128 (91)	744 (87)
Missing	1 (1)	0	1 (<1)	0	7 (2)	1 (1)	8 (1)
Enthesitis (LEI), n (%)							
Yes‡	36 (27)	106 (40)	142 (36)	70 (25)	143 (33)	36 (26)	249 (29)
No	96 (72)	161 (60)	257 (64)	211 (75.1)	282 (65.4)	103 (73.6)	596 (70.0)
Missing	1 (1)	0	1 (<1)	0	6 (1)	1 (1)	7 (1)
Bone erosion ≥1 or hs-CRP ≥6 mg/L or both							
n (%)	N/A	N/A	N/A	236 (84)	365 (85)	116 (83)	717 (84)

Source: Merola et al, 2023 (172); Merola et al, 2022 (189); BE COMPLETE Week 16 CSR (175); McInnes et al, 2023 (55); BE OPTIMAL Week 52 CSR (178).
†The presence of dactylitis was defined by a score greater than 0 on the LDI; dactylitic sites listed as digit eligible count for LDI; ‡The presence of enthesitis was defined by a score greater than 0 on the LEI; the LEI score corresponds to the number of enthesitic sites.
Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BKZ, bimekizumab; BMI, body mass index; BSA, body surface area; HAQ-DI, Health Assessment Questionnaire-Disability Index; hs-CRP, high sensitivity C-reactive protein; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; N/A, not applicable; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsA, psoriatic arthritis; PSO, psoriasis; QXW, every X weeks; RS, randomised set; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count.

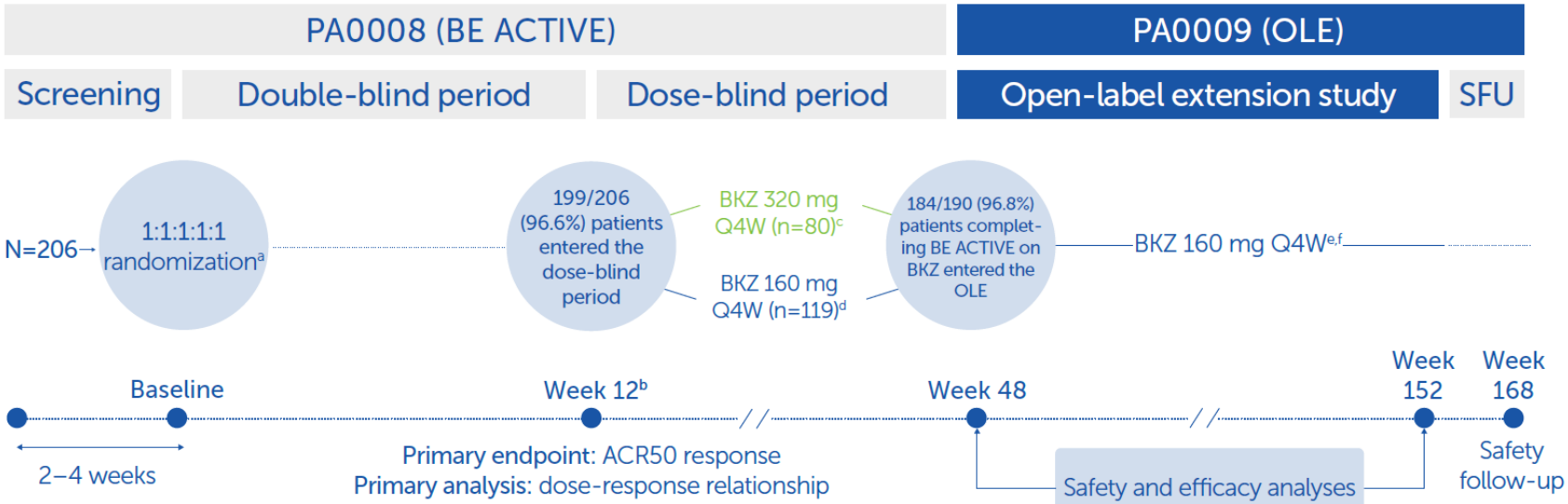
B.3.3.2 Supporting evidence

Long-term efficacy and safety supporting evidence comes from the Phase 2 study, BE ACTIVE and associated OLE study, BE ACTIVE 2.

B.3.3.2.1 BE ACTIVE and BE ACTIVE 2

An overview of the BE ACTIVE study design is presented in Figure 4 and Table 12. BE ACTIVE 2 was a multicentre OLE study evaluating the long-term safety and efficacy of bimekizumab 160 mg Q4W SC up to 3 years in patients with PsA who completed BE ACTIVE and enrolled in the OLE (184). In total, 184/206 (89.3%) patients enrolled in the OLE and 183 received ≥1 dose of bimekizumab. During the OLE 161/184 patients (87.5%) completed treatment to Week 152; 78.2% of all patients who started at Week 0 completed the full 152 weeks of treatment.

Figure 4: BE ACTIVE and BE ACTIVE 2: Study design



[a]At the start of the double-blind period, n=42 were assigned to PBO, n=41 to BKZ 16 mg Q4W, n=41 to BKZ 160 mg Q4W (320 mg LD), n=41 to BKZ 160 mg Q4W, n=41 to BKZ 320 mg Q4W; [b]After Week 12, patients receiving PBO or BKZ 16 mg were re-randomised (1:1) to receive BKZ 160 mg Q4W or BKZ 320 mg Q4W; all other patients continued on their previous dose; [c]Two patients initially receiving PBO, one receiving BKZ 16 mg Q4W and two receiving BKZ 320 mg Q4W discontinued prior to Week 48; [d]Three patients initially receiving BKZ 160 mg Q4W (320 mg LD) and one receiving BKZ 160 mg Q4W discontinued prior to Week 48; [e]N=181 for the full analysis set in the OLE; [f]N=183 for the safety set in the OLE.
Abbreviations: ACR, American College of Rheumatology; BKZ, bimekizumab; LD, loading dose; OLE, open-label extension; PBO, placebo; Q4W, every 4 weeks SFU, safety follow-up.

Table 12: BE ACTIVE: Overview of trial methodology

Trial name	BE ACTIVE (173, 182)
NCT #	NCT02969525
Objective	To evaluate the dose response based on the efficacy, safety and tolerability of bimekizumab in patients with active PsA
Location	Czech Republic, Germany, Hungary, Poland, Russia, and the USA
Status	Complete (July 2018)
Trial design	Phase 2b, multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study evaluating the efficacy and safety of bimekizumab in patients with active PsA
Duration of study	• Screening period: 14 to 28 days • Double blind period: 12 weeks (Week 1 to Week 12) • Dose-blind period: 36 weeks (Week 12 to Week 48) • SFU period: 20 weeks after final dose • Patients completing BE ACTIVE who did not qualify for rescue therapy during the dose-blind period were eligible to enter the open-label extension study BE ACTIVE 2
Methods of randomisation	• During the double-blind period, patients were randomised 1:1:1:1:1 (stratified by region and prior TNFi exposure) to receive: ○ Placebo ○ Bimekizumab 16 mg SC Q4W ○ Bimekizumab 160 mg SC Q4W ○ Bimekizumab 320 mg SC Q4W ○ Bimekizumab 320 mg LD followed by 160 mg SC starting at Week 4 and Q4W thereafter • At the Week 12 visit at the end of the double-blind period, patients were allocated to bimekizumab treatment regimens as follows: ○ Patients in the placebo group were re-randomised 1:1 to bimekizumab 160 mg or bimekizumab 320 mg Q4W ○ Patients in the bimekizumab 16 mg dose group were re-randomised 1:1 to bimekizumab 160 mg or bimekizumab 320 mg Q4W ○ Patients in the bimekizumab 160 mg dose group continued to receive bimekizumab 160 mg Q4W ○ Patients in the bimekizumab 320 mg dose group continued to receive bimekizumab 320 mg Q4W ○ Patients in the bimekizumab 320 mg (loading)/160 mg dose group continued to receive bimekizumab 160 mg Q4W
Key inclusion criteria	• ≥18 years old • Documented diagnosis of adult-onset, active PsA: ○ Meeting the CASPAR classification criteria for ≥6 months prior to screening ○ Baseline TJC ≥3 out of 78 and SJC ≥3 out of 76 (dactylitis of a digit counts as 1 joint each) • Negative for rheumatoid factor and anti-CCP antibodies • Active psoriatic lesion(s) and/or a documented history of PSO • Patients may have been TNFi-naïve or may have received one prior TNFi. Patients who were on prior TNFi must have:

<table>
<tr><td>Trial name</td><td>BE ACTIVE (173, 182)</td></tr>
<tr><td></td><td>

Experienced an inadequate response to previous treatment given for ≥3 months
Been intolerant to administration (e.g. had a side effect or AE leading to discontinuation)

</td></tr>
<tr><td>Baseline characteristics and demographics</td><td>
Baseline demographics and disease characteristics were generally well balanced between treatment arms

Baseline characteristics in BE ACTIVE
<table>
<tr><th></th><th>PBO

N=42</th><th>BKZ 16 mg

N=41</th><th>BKZ 160 mg

N=41</th><th>BKZ 160 mg w/ LD
N=41</th><th>BKZ 320 mg

N=41</th></tr>
<tr><td>Age, years (mean [SD])</td><td>49.02 (12.07)</td><td>49.98 (13.56)</td><td>48.00 (11.65)</td><td>49.05 (12.99)</td><td>50.39 (12.08)</td></tr>
<tr><td>Male, n (%)</td><td>24 (57.1)</td><td>24 (58.5)</td><td>20 (48.8)</td><td>14 (34.1)</td><td>23 (56.1)</td></tr>
<tr><td>Time since diagnosis, years (mean [SD])</td><td>6.71 (7.00)</td><td>7.01 (8.80)</td><td>7.09 (9.88)</td><td>7.94 (8.08)</td><td>6.97 (7.15)</td></tr>
<tr><td>PSO BSA ≥3%</td><td>28 (66.6)</td><td>29 (70.7)</td><td>28 (68.3)</td><td>26 (63.4)</td><td>26 (63.4)</td></tr>
<tr><td>Prior TNFi</td><td>9 (21.4)</td><td>7 (17.1)</td><td>8 (19.5)</td><td>7 (17.1)</td><td>8 (19.5)</td></tr>
</table>
</td></tr>
<tr><td>Analysis sets</td><td>

FAS (N=206)

Placebo n=42; bimekizumab 16 mg n=41; bimekizumab 160 mg n=41; bimekizumab 160 mg with LD n=41; bimekizumab 320 mg n=41

</td></tr>
<tr><td>Outcomes specified in the scope</td><td>

Disease activity: ACR20/50/70 to Week 152, PASI75/90/100 to Week 152, MDA to Week 152, VLDA to Week 152, Composite ACR50+PASI100 at Week 48, 96 and 152, PsARC at Week 48, 96, and 152
Periarticular disease: dactylitis resolution (LDI) to Week 152, enthesitis resolution (MASES) to Week 152
Functional capacity: HAQ-DI at Week 12, 48, 96, and 152
HRQoL: SF-36 PCS at Week 12, 48, 96, and 152
Adverse effects of treatment: AEs, including deaths

</td></tr>
</table>

Abbreviations: ACR, American College of Rheumatology; AE, adverse event; BKZ, bimekizumab; BSA, body surface area; CASPAR, Classification Criteria for Psoriatic Arthritis; CCP, cyclic citrullinated peptide; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; HRQoL, health-related quality of life; LD, loading dose, LDI, Leeds Dactylitis Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MDA, minimal disease activity; NCT, National Clinical Trial; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; PSO, psoriasis; Q4W; every 4 weeks; SC, subcutaneous; SD, standard deviation; SF-36 PCS, Short form-36 Physical Component Summary; SFU, safety follow-up; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor alpha inhibitor; TNFi, tumour necrosis factor alpha-inhibitor; USA, United States of America; VLDA, very low disease activity.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.3.4.1 Primary evidence

B.3.4.1.1 Analysis sets

The number of patients in each analysis set used for the outcomes relevant to this submission is provided in Table 13.

Table 13: BE COMPLETE and BE OPTIMAL: Analysis sets

Trial	BE COMPLETE			BE OPTIMAL			
Population	**PBO** **N=133** **n (%)**	**BKZ 160 mg Q4W** **N=267** **n (%)**	**Overall** **N=400** **n (%)**	**BKZ 160 mg Q4W** **N=431** **n (%)**	**ADA 40 mg Q2W reference arm†** **N=140** **n (%)**	**Overall** **N=852** **n (%)**	**PBO/BKZ 160 mg Q4W** **N=281** **n (%)**
RS: enrolled study participants that were randomised	133 (100)	267 (100)	400 (100)	431 (100)	140 (100)	852 (100)	281 (100)
SS: all study participants who received ≥1 dose of the IMP	132 (99.2)	267 (100)	399 (99.8)	431 (100)	140 (100)	852 (100)	281 (100)
RAS: all patients in the RS who received ≥1 dose of IMP and had a valid radiographic image of the hands and feet (with an assessment performed by at least two reviewers) at screening	–	–	–	420 (97.4)	135 (96.4)	824 (96.7)	269 (95.7)
AMS: all patients who had received ≥1 dose of active IMP (BKZ or ADA)‡	–	–	–	431 (100)	140 (100)	842 (98.8)	271 (96.4)

†The adalimumab referenced arm was not powered for statistical comparison vs bimekizumab or placebo; ‡Covered the analysis of data collected during the active medication periods (active treatment-blind period for patients randomised to placebo, the double-blind treatment period, and the active treatment-blind period for patients randomised to bimekizumab or adalimumab).
Abbreviations: ADA, adalimumab; AMS, active medication set; BKZ, bimekizumab; IMP, investigational medicinal product; PBO, placebo; QXW, every X weeks; RAS, radiographic set; RS, randomised set; SS, safety set.

B.3.4.1.1.1 Statistical analysis used to compare groups for primary and secondary outcomes

Efficacy endpoints were evaluated at all scheduled visits in accordance with the schedule of study assessments. The statistical methods used to compare groups for the primary and secondary outcomes are presented in Table 14. Analysis of the primary, secondary, and additional endpoints were based on the randomised set (RS; unless otherwise stated in Section B.3.6).

Table 14: BE COMPLETE and BE OPTIMAL: Statistical methods for analysis of primary and secondary outcomes

Trial	BE COMPLETE	BE OPTIMAL
Primary endpoint	The primary objective was to demonstrate the clinical efficacy of bimekizumab administered SC Q4W vs placebo, as assessed by ACR50 response: H1: ACR50 response superior to placebo	
Ranked secondary endpoints	The ranked secondary efficacy endpoint hypotheses tested the superiority of bimekizumab vs placebo: • H2: CFB in HAQ-DI superior to placebo • H3: PASI90 response superior to placebo in patients with PSO BSA ≥3% at baseline • H4: CFB in SF-36 PCS superior to placebo • H5: MDA superior to placebo	The ranked secondary efficacy endpoint hypotheses tested the superiority of bimekizumab vs placebo: • H2: CFB in HAQ-DI superior to placebo • H3: PASI90 response superior to placebo • H4: CFB in SF36-PCS superior to placebo • H5: MDA superior to placebo • H6: CFB in vdHmTSS† superior to placebo in patients with elevated hs-CRP and/or with ≥1 bone erosion (hs-CRP ≥6 mg/L and/or erosion positive) • H7: Enthesitis-free state superior to placebo (based on pooled BE COMPLETE and BE OPTIMAL Week 16 data) • H8: Dactylitis-free state superior to placebo (based on pooled BE COMPLETE and BE OPTIMAL Week 16 data) • H9: CFB in vdHmTSS‡ superior to placebo
Non-ranked secondary and other endpoints	No statistical hypotheses tested	
Statistical analysis	• A fixed sequence testing procedure was applied for the primary and ranked secondary endpoints; this accounts for multiplicity and controls the family-wise type I error rate at alpha=0.05 (2-sided) • The null hypothesis was that the conditional OR=1 for binary efficacy endpoints, and that there was no difference between treatment groups for continuous efficacy endpoints • The statistical testing of an endpoint could have been investigated only if the null hypothesis for the previous endpoint had been rejected (i.e. if p<0.05)	

Trial	BE COMPLETE	BE OPTIMAL
Sample size and power calculation	Sample sizes was calculated using a 2-sided 2-sample Chi-square test with continuity correction (190) for binary endpoints, and a 2-sided 2-group Satterthwaite t-test (191) for continuous endpoints	
	Primary endpoint: • The test for detecting statistical superiority of bimekizumab (n=260) vs placebo (n=130) based on ACR50 response at Week 16 has 96% power to detect a true treatment difference of 16% (OR=3.16) Ranked secondary endpoints: • Assumptions for power calculations of ranked secondary endpoints and for which supporting data were available in the TNFi-IR population were based on the results of BE ACTIVE and the SPIRIT-P2 studies • The power varied per endpoint; further detail is available in the CSR (175)	Primary endpoint: • The test for detecting statistical superiority of bimekizumab (n=420) vs placebo (n=280) based on ACR50 response at Week 16 has >99% power to detect a true treatment difference of 27.8% (OR=4.09) Ranked secondary endpoints: • Assumptions for power calculations of the ranked secondary endpoints, and for which supporting data exists, are based on the interim results of BE ACTIVE, FUTURE 1, FUTURE 2, FUTURE 5, and SPIRIT P1 studies The power varied per endpoint; further detail is available in the CSR (178)
Enthesitis and dactylitis pooling strategy	IN BE OPTIMAL, the number of patients with dactylitis and/or enthesitis at baseline was lower than that used for the a priori power calculation. To provide well powered, clinically interpretable results, these outcomes in BE OPTIMAL were replaced with pooled BE COMPLETE and BE OPTIMAL endpoints for dactylitis free-state, and enthesitis-free state (which is a more clinically meaningful endpoint than CFB). As BE COMPLETE does not have either endpoint in its hierarchy; pooling within the closed sequential testing procedure of BE OPTIMAL did not introduce any inflation of the type 1 error within the BE OPTIMAL hierarchy. As the pooling was done to achieve power similar to the original a priori power, there was no additional adjustment to the p-value to make it more conservative	
Data management and patient withdrawals	• Missing data for the primary and other binary endpoints at Week 16 were imputed using NRI • For continuous outcomes, missing data were imputed using MI. Hierarchical testing of ranked secondary continuous outcomes used RBMI, in which the MI model was based on data from the placebo group	

†The study planned to enrol a minimum of 45% of study participants positive for elevated hs-CRP (hs-CRP ≥6mg/L) and/or who have ≥1 bone erosion at screening; ‡Based on the overall population.
Abbreviations: ACR, American College of Rheumatology; BSA, body surface area; CFB, change from baseline; CSR, clinical study report; HAQ-DI, Health Assessment Questionnaire-Disability Index; hs-CRP, high sensitivity C-reactive protein; MDA, minimal disease activity; MI, multiple imputation; NRI, non-responder imputation; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PSO, psoriasis; Q4W, every 4 weeks; RBMI, reference-based multiple imputation; SC, subcutaneous; SF-36 PCS, Short Form-36 Physical Component Summary; TNFi-IR, tumour necrosis factor alpha inhibitor-inadequate response; vdHmTSS, van der Heijde Modified Total Sharp Score.

B.3.4.2 Participant flow

Participant flow for each trial is presented in Appendix D; patient disposition and discontinuation is presented in Table 15.

Table 15: BE COMPLETE and BE OPTIMAL: Patient disposition and discontinuations

	BE COMPLETE			BE OPTIMAL							
				Double-blind treatment period				Active-treatment blind period			
	PBO N=133 n (%)	BKZ 160 mg Q4W N=267 n (%)	All patients N=400 n (%)	PBO N=281 n (%)	BKZ 160 mg Q4W N=431 n (%)	ADA 40 mg Q2W N=140 n (%)	All patients N=852 n (%)	PBO/ BKZ† 160 mg Q4W N=271 n (%)	BKZ 160mg Q4W N=414 n (%)	ADA 40mg Q2W N=136 n (%)	All patients N=821 n (%)
Discontinued study/period	8 (6.0)	4 (1.5)	12 (3.0)	10 (3.6)	16 (3.7)	3 (2.1)	29 (3.4)	14 (5.2)	27 (6.5)	11 (8.1)	52 (6.3)
Discontinued due to AE	0	2 (0.7)	2 (0.5)	2 (0.7)	8 (1.9)	2 (1.4)	12 (1.4)	6 (2.2)	9 (2.2)	4 (2.9)	19 (2.3)
Entered the OLE study	122 (91.7)	256 (95.9)	378 (94.5)	N/A	N/A	N/A	N/A	254 (93.7)	379 (91.5)	121 (89.0)	754 (91.8)

†Patients receiving placebo study participants switched to BKZ 160 mg Q4W at/after Week 16.
Abbreviations: ADA, adalimumab; AE, adverse event; BKZ, bimekizumab; N/A, not applicable; OLE, open-label extension; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks.

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

Appendix D contains quality assessment of each of the trials identified in the SLR.

B.3.6 Clinical effectiveness results of the relevant studies

The primary and secondary efficacy endpoints were evaluated using a fixed-sequence testing procedure to account for multiplicity, and the results for both Phase 3 trials are summarised in Table 16. According to this procedure, the statistical testing of an endpoint was investigated only if the null hypothesis for the previous endpoint had been rejected (i.e. if $p<0.05$).

Table 16: BE COMPLETE and BE OPTIMAL: Summary of the multiple testing strategy and outcomes at Week 16 (RS††)

Trial	BE COMPLETE		BE OPTIMAL	
Hypothesis	**Point estimate vs PBO (95% CI)**	**p-value BKZ vs PBO‡,§**	**Point estimate vs PBO (95% CI)**	**p-value BKZ vs PBO‡,¶**
H1: ACR50 response superior to placebo (NRI)	OR: 11.1 (5.4, 23.0)	<0.001	OR: 7.1 (4.6, 10.9)	<0.001
H2: CFB in HAQ-DI superior to placebo (RBMI)	LSM difference: −0.33 (−0.42, −0.23)	<0.001	LSM difference: –0.19 (–0.25, –0.13)	<0.001
H3: PASI90 response superior to placebo in patients with PSO BSA ≥3% at baseline (NRI)	OR: 30.2 (12.4, 73.9)	<0.001	OR: 63.0 (22.2, 178.9)	<0.001
H4: CFB in SF-36 PCS superior to placebo (RBMI)	LSM difference: 6.0 (4.4, 7.7)	<0.001	LSM difference: 4.3 (3.2, 5.4)	<0.001
H5: MDA superior to placebo (NRI)	OR: 13.1 (6.1, 28.0)	<0.001	OR: 5.4 (3.7, 8.1)	<0.001
H6: CFB in vdHmTSS superior to placebo in patients with elevated hs-CRP and/or with ≥1 bone erosion (hs-CRP ≥6 mg/L and/or erosion positive) (RBMI)	–	–	LSM difference: –0.33 (–0.52, –0.13)	0.001
H7: Enthesitis-free state superior to placebo in patients with LEI>0 at baseline (based on pooled BE COMPLETE and BE OPTIMAL Week 16 data) (NRI)	–	–	OR: 1.9 (1.2, 3.1)	0.008
H8: Dactylitis-free state superior to placebo in patients with LDI>0 at baseline (based on pooled BE COMPLETE and BE OPTIMAL Week 16 data) (NRI)	–	–	OR: 3.4 (1.6, 7.6)	0.002
H9: CFB in vdHmTSS superior to placebo in the overall population (RBMI)	–	–	LSM difference: –0.28 (–0.45, –0.11)	0.001

Source: BE COMPLETE Week 16 CSR (182); BE OPTIMAL Week 52 CSR (178) and McInnes et al, 2023 (55).
‡Tests performed at a 2-sided alpha level of 0.05. The statistical testing of an endpoint could have been investigated only if the null hypothesis for the previous endpoint had been rejected (i.e. if p<0.05); ¶For binary endpoints (NRI): p-value obtained from logistic regression with treatment, bone erosion at baseline (except H7 and H8), study (for H7 and H8), and region as factor. Point estimates and CIs obtained from adjusted ORs. For continuous endpoints (Reference-Based MI): p-value obtained from ANCOVA with treatment, bone erosion at baseline, region as fixed effects and the baseline value as covariate. Point estimates and CIs obtained from the difference in LSMs from the ANCOVA; §For binary endpoints (NRI), p-values were obtained from logistic regression with treatment, prior TNFi exposure and region as factors. Point estimates and CIs obtained from the difference of adjusted ORs. For continuous endpoints (reference-based MI), p-values were obtained from ANCOVA with treatment, prior TNFi exposure and region as fixed effects and the baseline value as covariate. CIs obtained from the difference in LSMs from the ANCOVA; ††Radiographic set for the vdHmTSS CFB outcomes in BE OPTIMAL.
Abbreviations: ACR, American College of Rheumatology; BKZ, bimekizumab; BSA, body surface area; CFB, change from baseline; CI, confidence interval; HAQ-DI, Health Assessment Questionnaire-Disability Index; hs-CRP, high sensitivity C-reactive protein; LDI, Leeds dactylitis index; LEI, Leeds enthesitis index; LSM, least squares mean; MDA, minimal disease activity; NRI, non-responder imputation; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PBO, placebo; PCS, physical component summary; PSO, psoriasis; RBMI, reference-based multiple imputation; SF-36, short form-36; TNFi, tumour necrosis factor alpha inhibitor; vdHmTSS, van der Heijde modified total sharp score.

B.3.6.1 Primary evidence

B.3.6.1.1 BE COMPLETE

B.3.6.1.1.1 Primary endpoint: ACR50 responder rate at Week 16

In TNFi-IR patients, bimekizumab achieved the primary endpoint, demonstrating a superior ACR50 responder rate at Week 16 compared with placebo (43% vs 7%, respectively; OR: 11.1, p<0.001) (Table 17; Figure 5).

Table 17: BE COMPLETE: ACR50 responder rate at Week 16 including logistic regression (RS – NRI)

ACR50	PBO N=133	BKZ 160 mg Q4W N=267
Responders, n (%)	9 (7)	116 (43)
OR vs placebo (95% CI); p-value	–	11.1 (5.4, 23.0); p<0.001

Source: Merola et al, 2023 (172) and BE COMPLETE Week 16 CSR (182) .
OR, CI, and p-value generated using logistic regression with treatment, previous exposure to TNFi, and region as factors.
Abbreviations: ACR, American College of Rheumatology; BKZ, bimekizumab; CI, confidence interval; NRI, non-responder imputation; OR, odds ratio; PBO, placebo; Q4W, every 4 weeks; RS, randomised set; TNFi, tumour necrosis factor alpha inhibitor.

B.3.6.1.1.2 Ranked secondary endpoints

In patients who are TNFi-IR, bimekizumab showed clinically meaningful, statistically significant improvements vs the placebo group for all ranked secondary endpoints, including HAQ-DI, PASI90, SF-36 PCS, and MDA response rate (p<0.001 for all comparisons; Table 18).

Table 18: BE COMPLETE: Results of the key ranked secondary endpoints (RS)

Endpoint	PBO N=133	BKZ 160 mg Q4W N=267	Point estimate vs PBO (95% CI); p-value
CFB in HAQ-DI at Week 16 including ANCOVA (mean [SE]) (RBMI)	–0.07 (0.04)	–0.38 (0.03)	LSM difference: −0.33 (–0.42, −0.23); p<0.001
PASI90 response at Week 16 including logistic regression (in patients with PSO BSA ≥3% at baseline) (n [%]) (NRI)	6 (7) of 88	121 (69) of 176	OR: 30.2 (12.4, 73.9); p<0.001
SF36-PCS CFB at Week 16 including ANCOVA (mean [SE]) (RBMI)	1.4 (0.7)	7.3 (0.5)	LSM difference: 6.0 (4.4, 7.7); p<0.001
MDA response at Week 16 including logistic regression (n [%]) (NRI)	8 (6)	118 (44)	OR: 13.1 (6.1, 28.0); p<0.001

Source: Merola et al, 2023 (172) and BE COMPLETE Week 16 CSR (182).
For binary variables, ORs, CIs, and p values were generated using logistic regression with treatment, previous exposure to TNFi, and region as factors. For continuous variables, LSM, SEs, difference in LSM, and p-values were generated using ANCOVA with treatment, previous exposure to TNFi, and region as fixed effects and the baseline value of the outcome as covariate. Binary variables were calculated with NRI, and hierarchical continuous outcomes with reference-based MI.
Abbreviations: ANCOVA, analysis of covariance; BKZ, bimekizumab; BSA, body surface area; CFB, change from baseline; CI, confidence interval; HAQ-DI, health assessment questionnaire-disability index; LSM, least squares mean; MDA, minimal disease activity; NRI, non-responder imputation; OR, Odds ratio; PASI, psoriasis area and severity index; PBO, placebo; PSO, psoriasis; Q4W, every 4 weeks; RBMI, reference-based multiple imputation; RS, randomised set; SE, standard error; SF-36 PCS, short form-36 Physical Component Summary; TNFi, tumour necrosis factor alpha inhibitor.

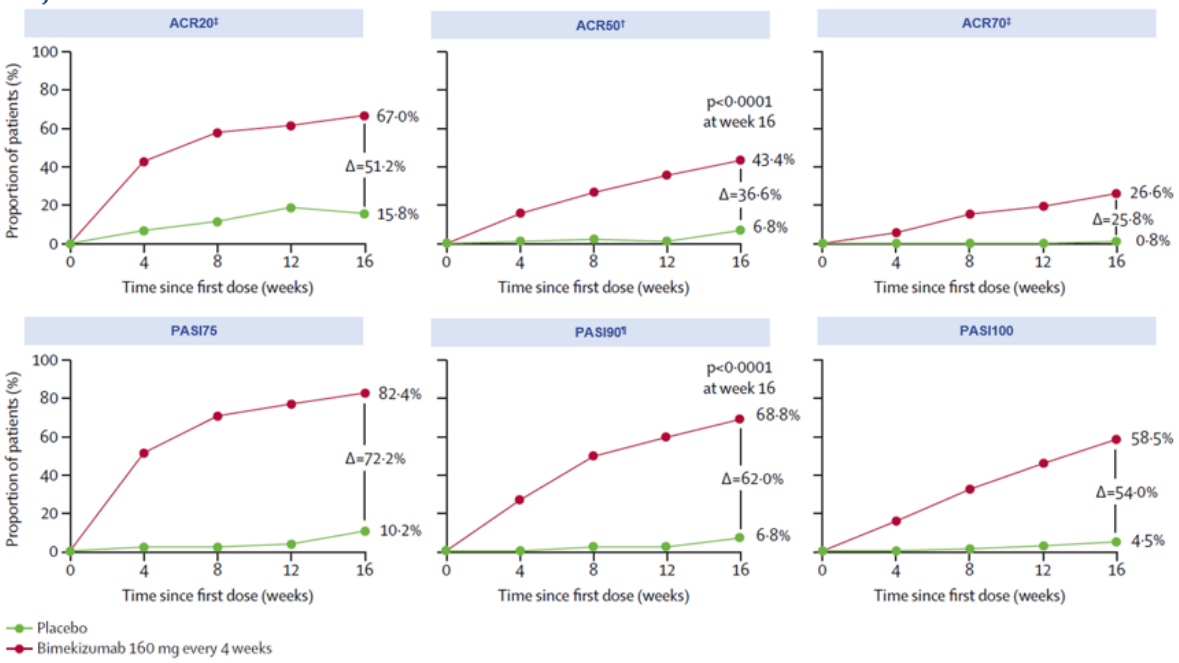
B.3.6.1.1.3 Non-ranked secondary and additional efficacy endpoints

B.3.6.1.1.3.1 Disease activity outcomes

At Week 16, the bimekizumab group had a higher ACR20 responder rate (a common primary endpoint in other PsA trials (39, 42, 43, 47, 49, 192)), and ACR70 responder rate (the most stringent ACR endpoint) vs the placebo group (nominal p<0.001 for both comparisons); these differences were considered clinically meaningful (Figure 5). ACR20, ACR50, and ACR70 responder rates were higher in those receiving bimekizumab treatment than in those receiving placebo as early as Week 4, after a single dose of bimekizumab (nominal p<0.001 for ACR20, and ACR50 [not evaluable for ACR70 due to a placebo response of zero] (176)).

In patients with PSO involving ≥3% BSA at baseline, 59% of patients receiving bimekizumab had complete skin clearance at Week 16 (as measured by PASI100), compared with 5% of patients receiving placebo (nominal p<0.001; Figure 5). A higher proportion of patients also achieved PASI75 at Week 16 (nominal p<0.001). Responder rates were numerically higher with bimekizumab than placebo as early as Week 4 for PASI75 (nominal p<0.001), PASI90, and PASI100 (nominal p-value not evaluable for both comparisons due to response of zero in the placebo group).

Figure 5: BE COMPLETE: ACR20, ACR50, ACR70 over time to Week 16, and PASI75, PASI90, and PASI100 over time to Week 16 in patients with PSO involving 3% BSA at baseline§ (RS – NRI)



Source: Merola et al, 2023 (172).
p-value for ACR50 (the primary endpoint) and PASI90 (key ranked secondary endpoint) at Week 16 generated with adjusted ORs.
†Primary endpoint at Week 16; ‡ACR20 and ACR70 at Week 16 are non-ranked secondary endpoints; nominal p<0.001 (not powered or adjusted for multiplicity); ¶PASI90 was a key ranked secondary endpoint at Week 16; §Placebo n=88; bimekizumab n=176.

Abbreviations: ACR, American College of Rheumatology; BSA, body surface area; NRI, non-responder imputation; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PSO, psoriasis; RS, randomised set.

Additionally, a greater proportion of patients receiving bimekizumab reached the ACR50+PASI100 (nominal p<0.001), and VLDA composite (nominal p=0.002) outcomes at Week 16 (Table 19). The PsARC responder rate, and proportion of patients achieving modified Nail Psoriasis Severity Index (mNAPSI) resolution (among patients with nail PSO at baseline [mNAPSI score >0]) were also numerically higher with bimekizumab vs placebo at Week 16 (nominal p<0.001 for both comparisons).

Table 19: BE COMPLETE: Other disease activity outcomes at Week 16 (RS – NRI)

Endpoint	PBO N=133	BKZ 160 mg Q4W N=267
Composite ACR50+PASI100 response by visit in patients with PSO involving at least 3% BSA at baseline (n [%])	1 (1) of 88	59 (34) of 176
PsARC response (n [%])	41 (30.8)	228 (85.4)
VLDA response (n [%])	3 (2)	36 (13)
Proportion of patients achieving mNAPSI resolution in the subgroup of patients with nail PSO at baseline† (n [%])	12 (14) of 83	73 (46) of 159

Source: Merola et al, 2023 (172); Sharma et al, 2023 (177); BE COMPLETE Week 16 CSR (175).
†mNAPSI score >0 at baseline.
Binary variables were calculated with NRI.
Abbreviations: ACR, American College of Rheumatology; BKZ, bimekizumab; BSA, body surface area; CFB, change from baseline; CSR, clinical study report; MI, multiple imputation; mNAPSI, modified Nail Psoriasis Severity Index; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; PSO, psoriasis; Q4W, every 4 weeks; VLDA, very low disease activity.

B.3.6.1.1.3.2 Axial outcomes

For the RS (multiple imputation [MI]), in patients with axial involvement at baseline (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥4), the mean baseline BASDAI scores in the placebo and bimekizumab groups were 6.49 (SE: 0.13) and 6.23 (SE: 0.09), respectively. Consistently greater mean reductions from baseline in BASDAI score were observed with bimekizumab than with placebo as early as Week 4 (–1.68 [SE: 0.14] vs –0.57 [SE: 0.16], respectively), and continued through Week 16 (–2.61 [SE: 0.15] vs –0.73 [0.20], respectively), demonstrating an improvement in axial disease.

B.3.6.1.1.4 Long-term BE COMPLETE data

After 52 weeks of treatment, 68.2%, 51.7%, and 35.6% of patients receiving bimekizumab had ACR20, ACR50, or ACR70 response (Table 20). In the subgroup of patients with PSO BSA ≥3% at baseline, 84.1%, 74.4%, and 65.9% continued to show PASI75, PASI90, or PASI100 response. A high proportion of patients also achieved PsARC response (80.1%), and the proportion of patients achieving MDA response was maintained to Week 52 (47.2%). Improvements in HAQ-DI were further increased to Week 52 (change from baseline at Week 16: –0.38; change from baseline at Week 52: –0.41).

Furthermore, high proportions of patients in the placebo arm who switched to bimekizumab 160 mg Q4W at/after Week 16 also achieved clinically meaningful improvements across these outcomes.

Table 20: BE COMPLETE: Long-term data

Endpoint	PBO/BKZ 160 mg Q4W† N=133	BKZ 160 mg Q4W N=267
ACR20 response at Week 52 (n [%]) (NRI)	80 (60.2)	182 (68.2)
ACR50 response at Week 52 (n [%]) (NRI)	54 (40.6)	138 (51.7)
ACR70 response at Week 52 (n [%]) (NRI)	34 (25.6)	95 (35.6)
PASI75 response (in patients with PSO BSA ≥3% at baseline) at Week 52 (n [%]) (NRI)	71 (80.7)	148 (84.1)
PASI90 response (in patients with PSO BSA ≥3% at baseline) at Week 52 (n [%]) (NRI)	65 (73.9)	131 (74.4)
PASI100 response (in patients with PSO BSA ≥3% at baseline) at Week 52 (n [%]) (NRI)	53 (60.2)	116 (65.9)
PsARC response at Week 52 (n [%]) (NRI)	98 (73.7)	214 (80.1)
MDA response at Week 52 (n [%]) (NRI)	44 (33.1)	126 (47.2)
CFB in HAQ-DI at Week 52 (mean [SD]) (OC)	–0.38 (0.60)	–0.41 (0.50)
SF-36 PCS at Week 40‡ (mean [SE]) (MI)	7.3 (0.9)	8.4 (0.6)

Source: UCB data on file 2023 (181)
Binary variables were calculated with NRI.
†Placebo patients switched to bimekizumab 160 mg Q4W at/after Week 16; ‡Week 52 data not available.
Abbreviations: ACR, American College of Rheumatology; BKZ, bimekizumab; CFB, change from baseline; HAQ-DI, Health Assessment Questionnaire – Disability Index; MDA, minimal disease activity; MI, multiple imputation; NRI, non-responder imputation; OC, observed case; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; Q4W, every 4 weeks; SD, standard deviation; SE, standard error SF-36 PCS, short-form-36 physical component summary.

B.3.6.1.2 BE OPTIMAL

B.3.6.1.2.1 Primary endpoint: ACR50 responder rate at Week 16

In bDMARD-naïve patients, bimekizumab achieved the primary endpoint, demonstrating a superior ACR50 responder rate at Week 16 vs placebo (44% vs 10%; OR: 7.1; p<0.001; Table 21). Longer-term data to Week 52 is presented in Figure 6, Section B.3.6.1.2.3.1.

Table 21: BE OPTIMAL: ACR50 responder rate at Week 16 including logistic regression (RS – NRI)

ACR50	PBO N=281	BKZ 160 mg Q4W N=431	ADA 40 mg Q2W reference arm† N=140
Responders, n (%)	28 (10)	189 (44)	64 (46)
OR vs PBO (95% CI)	–	7.1 (4.6, 10.9); p<0.001	–

Source: McInnes et al, 2023 (55) and BE OPTIMAL Week 52 CSR (178).
ORs, CIs, and p values were generated using logistic regression with treatment, bone erosion at baseline, and region as factors. Proportions were calculated using NRI. †The adalimumab reference arm was not powered for statistical comparisons with bimekizumab or placebo.
Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; BKZ, bimekizumab; CI, confidence interval; NRI, non-responder imputation; OR, odds ratio; PBO, placebo; QXW, very X weeks; RS, randomised set.

B.3.6.1.2.2 Ranked secondary endpoints

In BE OPTIMAL, hierarchical testing of continuous ranked secondary endpoints (change from baseline in HAQ-DI, SF-36 PCS, van der Heijde modified Total Sharp Score [vdHmTSS]) was performed using reference-based MI, in which the multiple imputation model was based on data from the placebo group. This analysis was performed only for patients randomised to bimekizumab, and placebo. Results of the reference-based MI analysis of continuous ranked secondary endpoints are presented in Table 16. In this section, in Table 22, results using MI for missing data are presented for continuous endpoints in order to allow the presentation of data from the adalimumab arm, however the p-values presented in this section for the ranked continuous outcomes are from the reference-based MI analyses.

In bDMARD-naïve patients, bimekizumab achieved a statistically significant improvement vs the placebo group at Week 16 in the change from baseline in HAQ-DI, SF-36 PCS, and significantly greater MDA response at Week 16 ($p<0.001$ for all comparisons) (Table 22). Patients in the bimekizumab group with PSO BSA ≥3% at baseline also had a statistically significantly higher PASI90 response vs placebo at Week 16 ($p<0.001$). In a subgroup of patients at risk of structural progression (i.e. hs-CRP ≥6 mg/L or ≥1 baseline bone erosions, or both [Section B.1.3.1.1.1]), and in the overall population, patients receiving bimekizumab had a minimal change from baseline in vdHmTSS, while the placebo group worsened at Week 16 ($p=0.001$ for both comparisons), therefore demonstrating significantly less structural progression on bimekizumab treatment.

Due to reduced statistical power for periarticular disease outcomes in the single trial population in BE OPTIMAL, a pooled population of bDMARD-naïve and TNFi-IR patients from BE COMPLETE and BE OPTIMAL was used to investigate the proportion of patients with enthesitis, or dactylitis at baseline who achieved an enthesitis-free, or dactylitis-free state, respectively at Week 16 (these endpoints were included in the statistical hierarchy for BE OPTIMAL). In this pooled population, a significantly higher proportion of patients in the bimekizumab group achieved complete resolution of enthesitis, and dactylitis vs placebo ($p=0.008$, $p=0.002$, respectively) at Week 16 (Table 22).

Table 22: BE OPTIMAL: Results of the ranked secondary endpoints

Endpoint	PBO N=281	BKZ 160 mg Q4W N=431	ADA 40 mg Q2W reference arm[†] N=140
HAQ-DI CFB at Week 16 including ANCOVA (RS – MI)			
Mean (SE)	–0.09 (0.03)	–0.26 (0.02)	–0.33 (0.04)
LSM difference BKZ vs PBO (95% CI)	–	–0.19 (–0.26, –0.13); p<0.001	–

Endpoint	PBO N=281	BKZ 160 mg Q4W N=431	ADA 40 mg Q2W reference arm† N=140
PASI90 response at Week 16 (in patients with PSO BSA ≥3% at baseline) (RS – NRI)			
Responders, n (%)	4 (3) of 140	133 (61) of 217	28 (41) of 68
OR BKZ vs PBO (95% CI)	–	63.0 (22.2, 178.9); p<0.001	–
SF36-PCS CFB at Week 16 including ANCOVA (RS – MI)			
Mean (SE)	2.3 (0.5)	6.3 (0.4)	6.8 (0.8)
LSM difference BKZ vs PBO (95% CI)	–	4.5 (3.4, 5.7); p<0.001	–
MDA response at Week 16 including logistic regression (RS – NRI)			
Responders, n (%)	37 (13)	194 (45)	63 (45)
OR BKZ vs PBO (95% CI)	–	5.4 (3.7, 8.1); <0.001	–
vdHmTSS CFB at Week 16 including ANCOVA in patients with elevated hs-CRP or ≥1 bone erosion at baseline (RAS – MI)			
Mean (SE); number of patients	0.36 (0.10); 227	–0.01 (0.04); 361	–0.05 (0.08); 112
LSM difference BKZ vs PBO (95% CI)	–	–0.35 (–0.54, –0.17); p=0.001	–
Enthesitis-free state (based on LEI) at Week 16 including logistic regression in patients with enthesitis at baseline (pooled BE COMPLETE and BE OPTIMAL‡) (RS – NRI)			
Responders, n (%)	37 (35) of 106	124 (50) of 249	18 (50) of 36
OR BKZ vs PBO (95% CI)	–	1.9 (1.2, 3.1); p=0.008	–
Dactylitis-free state (based on LDI) at Week 16 including logistic regression in patients with dactylitis at baseline (pooled BE COMPLETE and BE OPTIMAL‡) (RS – NRI)			
Responders, n (%)	24 (51) of 47	68 (76) of 90	9 (82) of 11
OR BKZ vs PBO (95% CI)	–	3.4 (1.6, 7.6); p=0.002	–
vdHmTSS CFB at Week 16 including ANCOVA (all patients) (RAS – MI)			
Mean (SE)	0.31 (0.09); 269	0.01 (0.04); 420	–0.03 (0.07); 135
LSM difference BKZ vs PBO (95% CI)	–	–0.30 (–0.46, –0.14); p=0.001	–

Source: McInnes et al, 2023 (55) and BE OPTIMAL Week 52 CSR (178).
For binary variables, ORs, CIs, and p-values were generated using logistic regression with treatment, bone erosion at baseline, and region as factors. For enthesitis and dactylitis resolution, where data were pooled from BE COMPLETE and BE OPTIMAL, the study was also included as a factor in the model, and bone erosion at baseline was excluded. For continuous variables, LSM, SE, difference in LSM, and p-values were generated using ANCOVA with treatment, bone erosion at baseline, and region as fixed effects, and the baseline value as covariate. Continuous variables were calculated using MI. Reference-based MI was used in hierarchical testing. Proportions were calculated using NRI. †The adalimumab reference arm was not powered for statistical comparisons with bimekizumab or placebo; ‡Data for the placebo and bimekizumab groups are pooled from the BE OPTIMAL and BE COMPLETE trials; data for patients in the reference group are reported from BE OPTIMAL only.
Abbreviations: ADA, adalimumab; ANCOVA, analysis of covariance; BKZ, bimekizumab; BSA, body surface area; CFB, change from baseline; CI, confidence interval; HAQ-DI, Health Assessment Questionnaire-Disability index; hs-CRP, high sensitivity C-reactive protein; LDI, Leeds Dactylitis Index; Leeds Enthesitis Index; LSM, lease squares mean; MDA, minimal disease activity; MI, multiple imputation; NRI, non-responder imputation; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PBO, placebo; PSO, psoriasis; QXW, every X weeks; RAS, radiographic set; RS, randomised set; SE, standard error; SF-36 PCS, short form-36 physical component summary; vdHmTSS, van der Heidje modified total Sharp score.

B.3.6.1.2.3 Non-ranked secondary, additional efficacy, and long-term endpoints

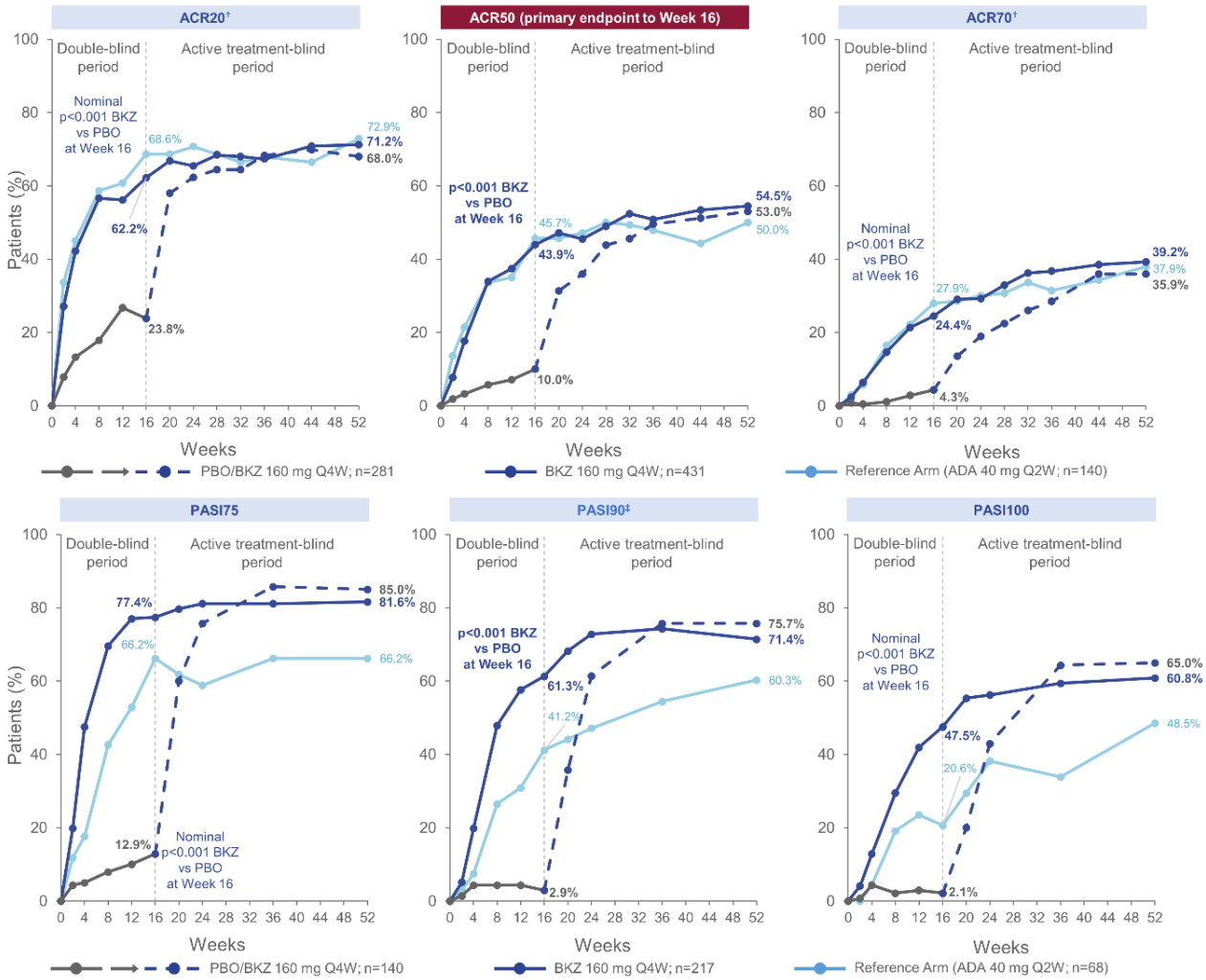
B.3.6.1.2.3.1 Disease activity outcomes

At Week 16, a higher proportion of patients achieved ACR20 (a common endpoint in PsA trials (39, 42, 43, 47, 49, 192)), and ACR70 response (the most stringent ACR endpoint) vs placebo (nominal p<0.001 for both comparisons; Figure 6). In addition, a higher proportion of patients (in the subgroup with PSO BSA ≥3% at baseline) achieved PASI75, PASI90, and PASI100 at Week 16 vs placebo (PASI75, and PASI100 nominal p<0.001; PASI90 [key ranked secondary endpoint] p<0.001). Notably, almost half (47.5%) of these patients achieved complete skin clearance (PASI100) at Week 16.

The differences in responder rates between bimekizumab and placebo occurred as early as Week 2 for ACR20 (nominal p<0.001), ACR50 (nominal p=0.002), and PASI75 (nominal p<0.001), and Week 4 for all ACR and PASI criteria (nominal p<0.001 for ACR20, ACR50, PASI75, PASI90; nominal p=0.004 for ACR70; nominal p=0.006 for PASI100 at Week 4). Continued improvements/sustained joint, and skin responses with bimekizumab were demonstrated to Week 52. Patients who switched from placebo to bimekizumab at Week 16 also showed response as early as Week 4, and the response was sustained to Week 52. For ACR50, in patients who had an observed response at Week 16 with bimekizumab, the ACR50 response was maintained in 87.2% of responders up to Week 52. The median time to ACR criteria response with bimekizumab vs placebo was:

- ACR20: 8 weeks vs. 16.43 weeks
- ACR50: 16 weeks vs non calculable
- ACR70: 17.57 weeks vs not calculable.

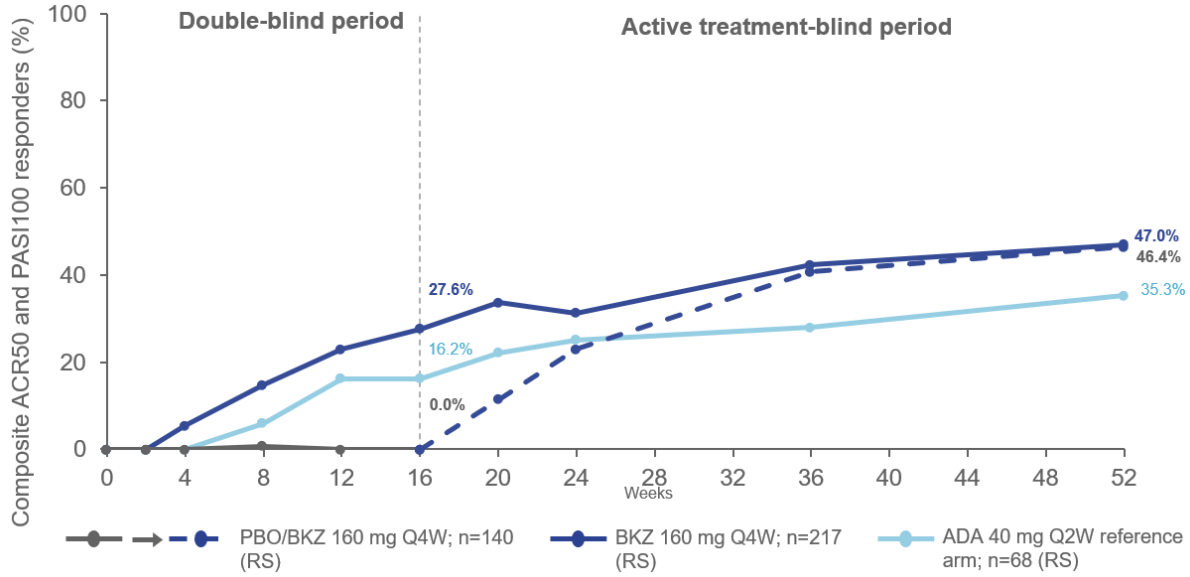
Figure 6: BE OPTIMAL: ACR20, ACR50 and ACR70 over time to Week 52, and PASI75, PASI90, and PASI100 over time to Week 52 in patients with PSO involving ≥3% BSA at baseline (RS – NRI)



Source: Ritchlin et al, 2022 (179).
p-value calculated using a logistic regression model with treatment, bone erosion at baseline, and region as stratification factors. Nominal p-values are not powered or adjusted for multiplicity and should not be used to assess statistical significance. The adalimumab reference arm was not powered for statistical comparisons with bimekizumab or placebo.
†ACR20 and ACR70 at Week 16 are non-ranked secondary endpoints; ‡PASI90 was a key ranked secondary endpoint at Week 16; PASI90 at Week 4 was a non-ranked secondary efficacy endpoint.
Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; BKZ, bimekizumab; BSA, body surface area; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PBO, placebo; PSO, psoriasis; Q4W, every 4 weeks; RS, randomised set.

For the composite ACR50+PASI100 outcome (i.e. combined skin and joint response) in patients with PSO BSA ≥3% at baseline, a numerically higher responder rate vs placebo was observed as early as Week 4 (nominal p not evaluable), with a clinically meaningful difference observed from Week 8 and continuing to improve to Week 52 (Figure 7). A response within 4 weeks was also observed in patients switching from placebo to bimekizumab at Week 16.

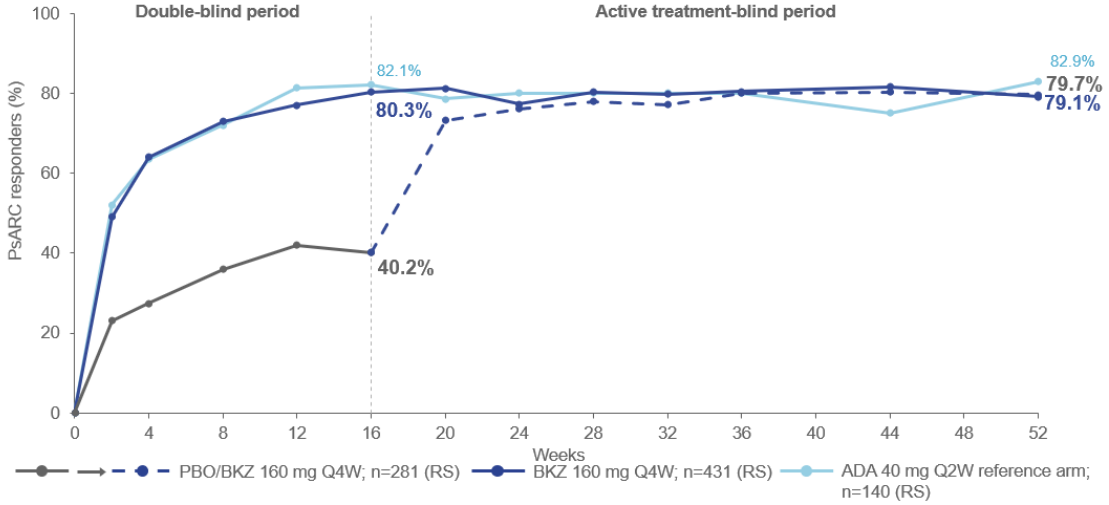
Figure 7: BE OPTIMAL: Composite ACR50+PASI100 over time to Week 52 in patients with PSO involving ≥3% BSA at baseline (RS – NRI)



Source: BE OPTIMAL Week 52 CSR (178).
The adalimumab reference arm was not powered for statistical comparisons with bimekizumab or placebo.
Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; BKZ, bimekizumab; BSA, body surface area; NRI, non-responder imputation; PASI, psoriasis area and severity index; PBO, placebo; PSO, psoriasis; QXW, every X weeks; RS, randomised set.

The PsARC responder rate was higher with bimekizumab than placebo as early as Week 2 (nominal p<0.001) after a single dose (Figure 8), increased for the bimekizumab group through Week 16, and was higher vs placebo at each timepoint (all nominal p<0.001). The PsARC response with bimekizumab treatment was sustained up to Week 52. There was a notable increase in PsARC responder rate from Week 16 to Week 24 in patients who switched from placebo to bimekizumab at Week 16, and this response was maintained to Week 52.

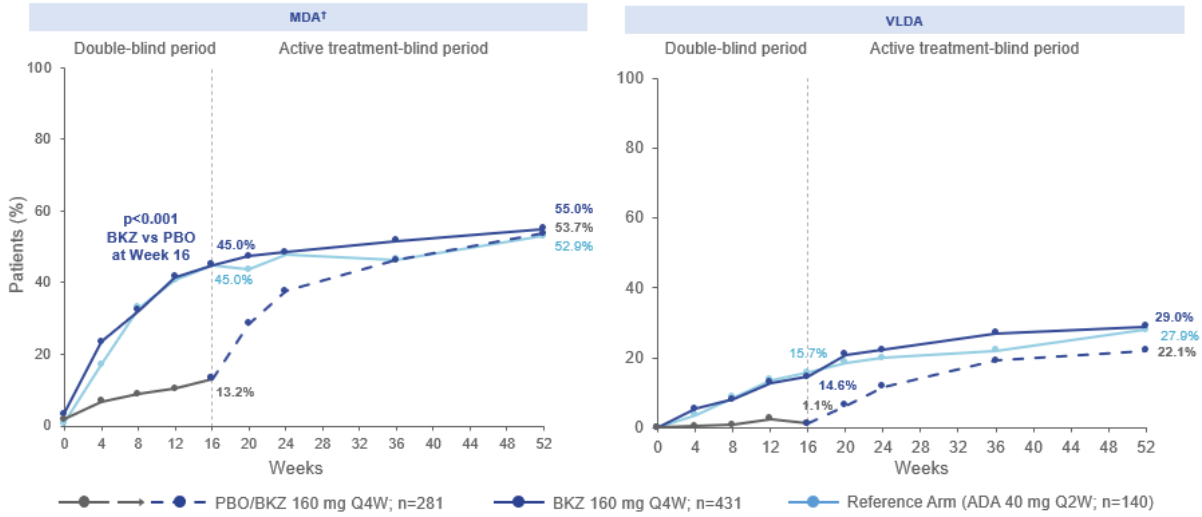
Figure 8: BE OPTIMAL: PsARC over time to Week 52 (NRI)



Source: BE OPTIMAL Week 52 CSR (178).
The adalimumab reference arm was not powered for statistical comparisons with bimekizumab or placebo.
Abbreviations: ADA, adalimumab; BKZ, bimekizumab; NRI, non-responder imputation; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; QXW, every X weeks; RS, randomised set.

As early as Week 4, the MDA responder rate was higher in the bimekizumab group than the placebo group (nominal p<0.001), increased through to Week 16, and was higher with bimekizumab at each time point (all nominal p<0.001) (Figure 9). The MDA response with bimekizumab treatment continued to improve to 55% at Week 52. At Week 4, the VLDA responder rate was also higher with bimekizumab treatment vs placebo, with clinically meaningful differences observed at Week 12 and Week 16; the VLDA responder rate continued to improve with bimekizumab to Week 52 (Figure 9). In patients switching from placebo to bimekizumab, the MDA and VLDA responder rates increased from Week 16 to Week 52.

Figure 9: BE OPTIMAL: MDA, and VLDA over time to Week 52 (RS – NRI)



Source: Source: Ritchlin et al, 2022 (179) and BE OPTIMAL Week 52 CSR (178).
†Key ranked secondary endpoint at Week 16.
p-value for MDA calculated using a logistic regression model with treatment, bone erosion at baseline, and region as stratification factors. The adalimumab reference arm was not powered for statistical comparisons with bimekizumab or placebo.
Abbreviations: ADA, adalimumab; BKZ, bimekizumab; MDA, minimal disease activity; NRI, non-responder imputation; PBO, placebo; QXW, every X weeks; RS, randomised set; VLDA, very low disease activity.

In patients with nail PSO at baseline (mNAPSI score >0), the proportion of patients achieving mNAPSI resolution was 33.6% with bimekizumab vs 18.6% with placebo at Week 16 (nominal p=0.002). The proportion of patients achieving mNAPSI resolution with bimekizumab treatment continued to improve to 65.6% at Week 52. In patients who switched from placebo to bimekizumab at Week 16, the proportion of patients achieving mNAPSI resolution increased notably from Week 16, and was similar to the bimekizumab group by Week 52 (71.2%).

B.3.6.1.2.3.2 Axial outcomes

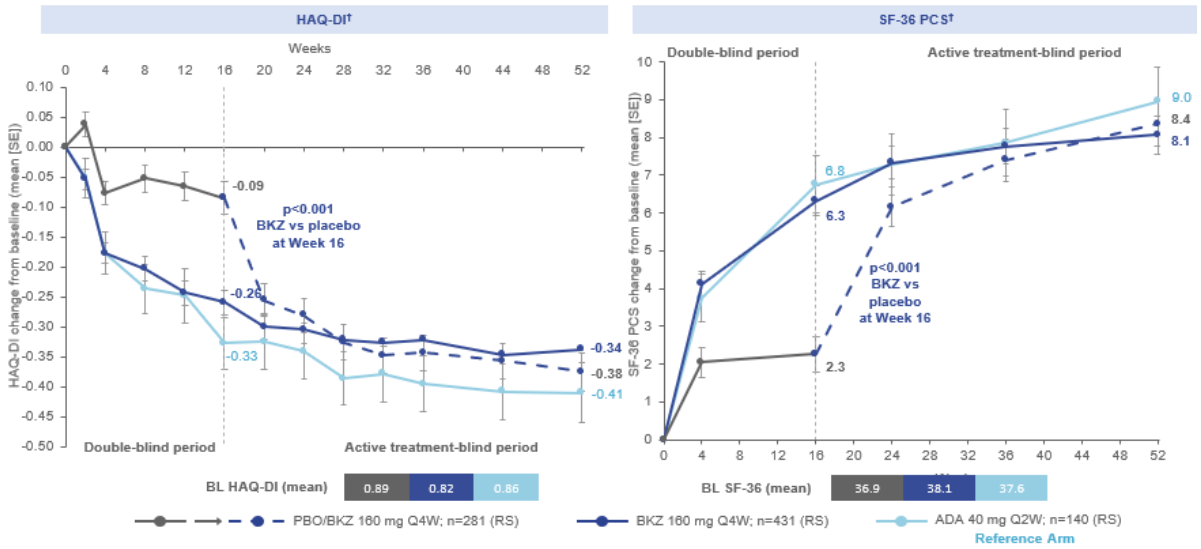
For the RS (MI), in patients with axial involvement (BASDAI ≥4 at baseline), a greater mean reduction from baseline in BASDAI score was observed in the bimekizumab group vs the placebo group as early as Week 4 (–1.70 [SE: 0.11] vs –0.76 [SE: 0.11], respectively), with a further reduction to Week 16 (–2.55 [SE: 0.12] vs –1.06 [SE: 0.14], respectively); the

improvement with bimekizumab treatment was sustained up to Week 52 (–3.21 [SE: 0.12]). In patients who switched from placebo to bimekizumab at Week 16, the mean reduction in BASDAI score improved from Week 16 to Week 52 (–2.97 [SE: 0.17]), demonstrating an improvement in axial disease (180).

B.3.6.1.2.3.3 HRQoL/functional outcomes

Functional outcomes improved in the bimekizumab group, with a greater mean reduction vs placebo in HAQ-DI score observed as early as Week 2, and greater improvement in mean SF-36 PCS score vs placebo observed as early as Week 4 (this difference was clinically meaningful (i.e. >2 points (193)). The improvements in HAQ-DI score, and SF-36 PCS score with bimekizumab continued through Week 16, and were sustained to Week 52. In patients who switched from placebo to bimekizumab 160 mg Q4W at Week 16, the mean reduction in HAQ-DI score, and mean SF-36 PCS score, improved from Week 16 to Week 52.

Figure 10: BE OPTIMAL: Change from baseline in HAQ-DI, and SF-36 PCS to Week 52 (RS – MI)



Source: BE OPTIMAL Week 52 CSR (178) and BE OPTIMAL Week 52 CSR TFLs (180).
Continuous variables were calculated using MI. Reference-based MI was used in hierarchical testing.
p-value was calculated using ANCOVA with treatment, bone erosion at baseline, and region as fixed effects and baseline values as covariate. The adalimumab reference arm was not powered for statistical comparisons with bimekizumab or placebo. †Key ranked secondary endpoint at Week 16.
Abbreviations: ADA, adalimumab; ANCOVA, analysis of covariance; BKZ, bimekizumab; HAQ-DI, Health Assessment Questionnaire-Disability Index; MI, multiple imputation; PBO, placebo; QXW, every x weeks; RS, randomised set; SE, standard error; SF-36 PCS, Short form-36 Physical Component Summary.

B.3.6.1.2.3.4 Disease progression

During the study, radiographic progression was minimal to Week 52 in the majority of patients treated with bimekizumab. The proportion of patients with no radiographic joint damage progression (defined as a change from baseline vdHmTSS of ≤0.5%) was higher with bimekizumab vs placebo at Week 16 (Table 23). At Week 52, more than three-quarters of

patients in the bimekizumab group, and of those who switched to bimekizumab at Week 16 had no radiographic joint damage progression.

Table 23: BE OPTIMAL: Proportion of patients with no radiographic progression from baseline to Week 16 and Week 52 (vdHmTSS change from baseline ≤0.5%) (RAS – NRI)

	PBO/BKZ 160 mg Q4W	BKZ 160 mg Q4W	ADA 40 mg Q2W reference arm† N=140
Overall population			
N	269	420	135
Week 16, n (%)	222 (82.5)	356 (84.8)	109 (80.7)
Week 52, n (%)	207 (77.0)	326 (77.6)	111 (82.2)

Source: BE OPTIMAL Week 52 CSR (178).
NRI used the estimated approach. Missing data or data after study treatment discontinuation were set to nonresponse.
†The adalimumab reference arm was not powered for statistical comparisons with bimekizumab or placebo.
Abbreviations: ADA, adalimumab; BKZ, bimekizumab; NRI, non-responder imputation; PBO, placebo; QXW, every X weeks; RAS, radiographic set; vdHmTSS, van der Heidje-modified Total Sharp Score.

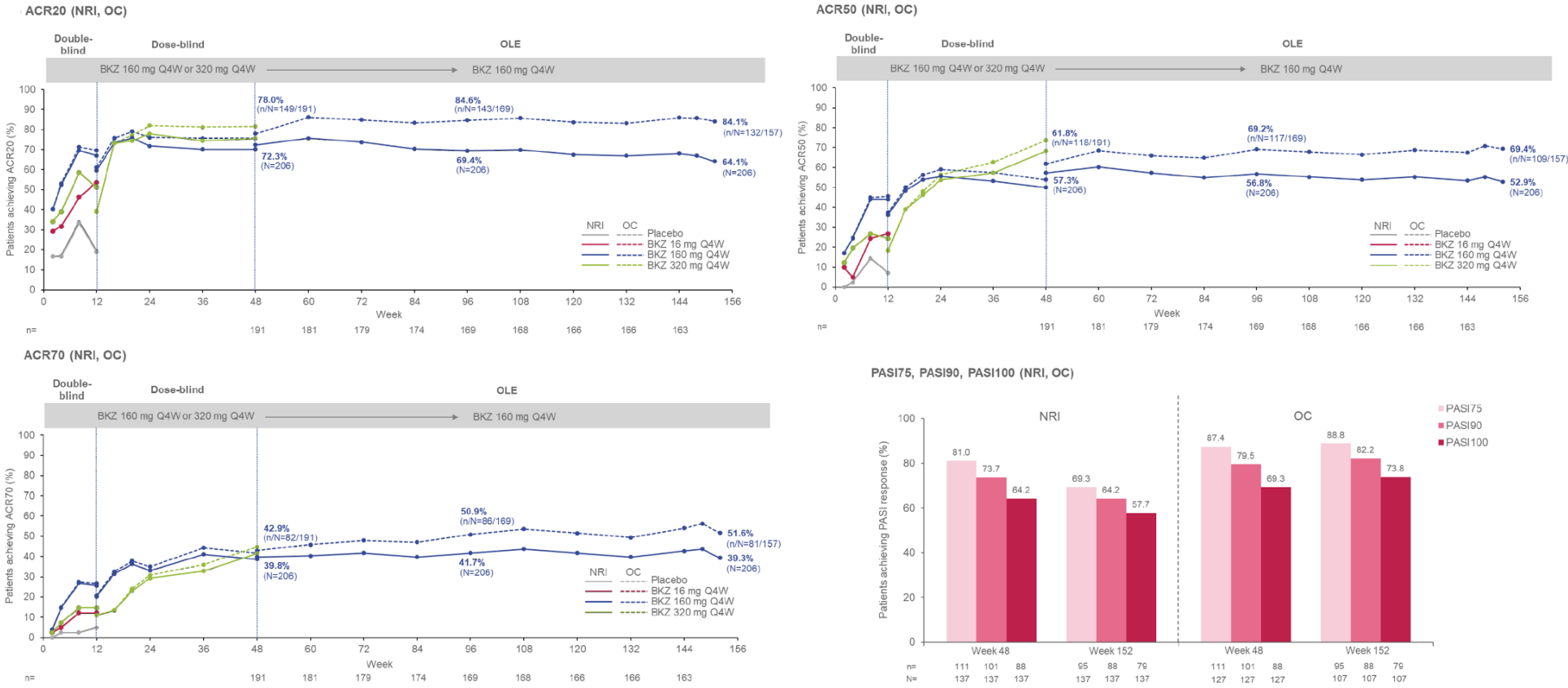
B.3.6.2 Supporting evidence

B.3.6.2.1 BE ACTIVE and BE ACTIVE 2

In the Phase 2 study BE ACTIVE, at the end of the double-blind period (12 weeks), a greater proportion of patients receiving bimekizumab 160 mg Q4W achieved the primary, and secondary endpoints vs placebo (ACR50 [primary] nominal p=0.0012; ACR20 nominal p<0.0001; ACR70 nominal p<0.065; PASI75 nominal p=0.0001; PASI90 nominal p=0.0020). A higher proportion of patients also achieved PASI100, and MDA, with greater improvements in SF-36 PCS, and HAQ-DI scores, and a higher PsARC responder rate at Week 12 (Appendix L). The response with bimekizumab 160 mg Q4W was maintained to the end of the dose-blind period (Week 48).

Results of selected outcomes from the OLE study BE ACTIVE 2 (where after the end of the BE ACTIVE dose-blind period, patients received bimekizumab for a further 104 weeks, totalling 152 weeks of treatment) are presented in Figure 11, Figure 12, and Table 24. Improvements in outcomes were observed as early as Week 4, and sustained over 3 years of treatment with bimekizumab, and there was no worsening of disease in patients who dosed down from bimekizumab 320 mg to 160 mg in the OLE.

Figure 11: BE ACTIVE and BE ACTIVE 2: ACR20, ACR50, ACR70, PASI75, PASI90, and PASI100 (NRI, OC)

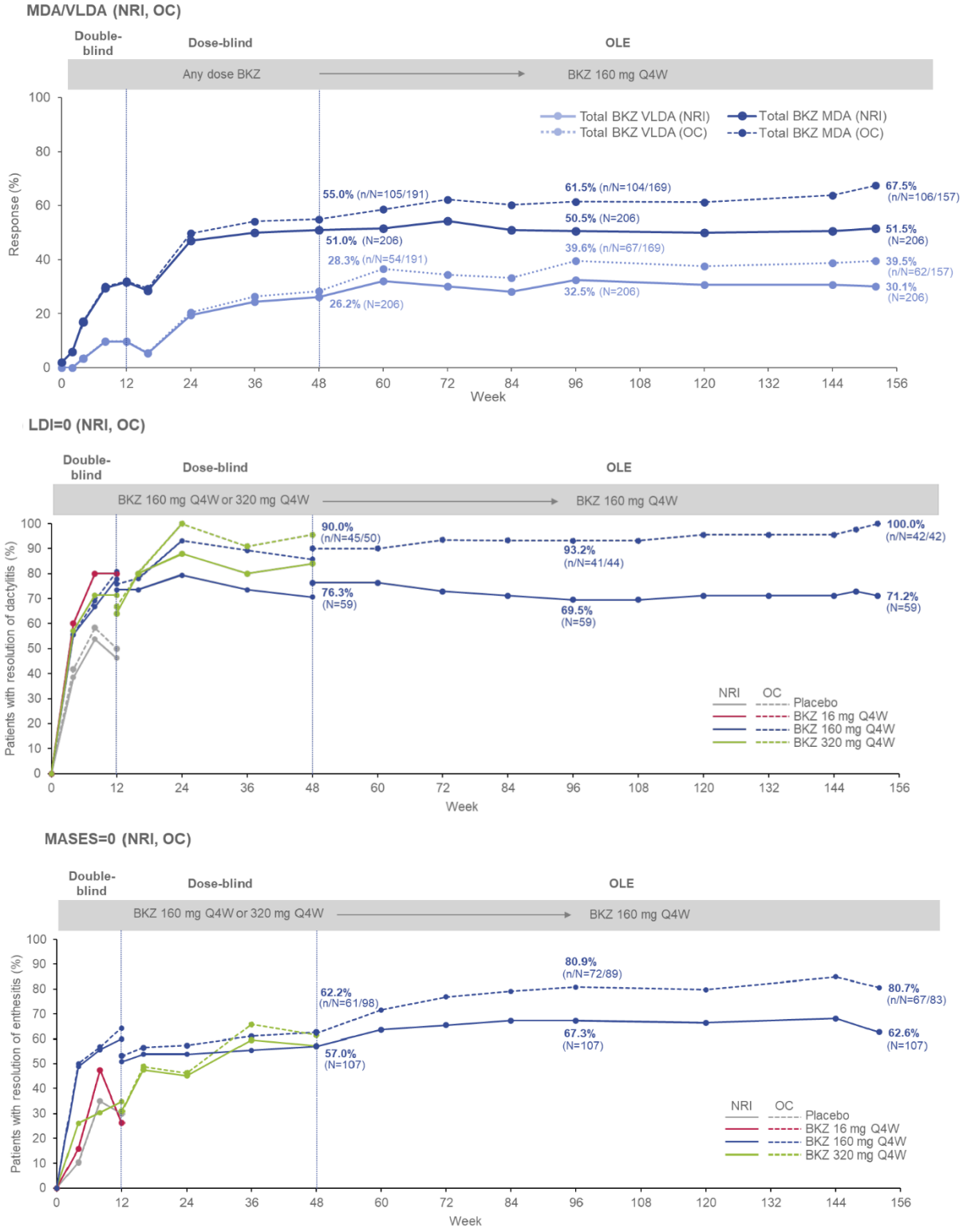


Source: Coates et al, 2022 (174).

Patients randomised to receive placebo, bimekizumab 16 mg Q4W, or bimekizumab 320 mg Q4W through the double-blind period are shown, and patients assigned to bimekizumab 160 mg Q4W with or without a 320 mg LD at double-blind period entry are combined for weeks 0–12. Percentages in the dose-blind period include those assigned bimekizumab 160 mg Q4W with or without a 320 mg LD, or bimekizumab 320 mg Q4W at double-blind period entry, as well as those assigned to placebo or bimekizumab 160 mg Q4W who were re-randomised to 160 mg or 320 mg bimekizumab Q4W. All OLE study patients received 160 mg of bimekizumab Q4W regardless of prior dosing regimen; 157 patients had an efficacy assessment at week 152. All OLE study patients received bimekizumab 160 mg Q4W regardless of prior dosing regimen. At baseline of the double-blind period, 137 patients had ≥3% BSA affected by PSO; due to a data collection error and lack of data from the study visit, Week 96 data are not reported for PASI. Circles represent timepoints at which patients were assessed.

Abbreviations: ACR, American College of Rheumatology; BKZ, bimekizumab; BSA, body surface area; LD, loading dose; NRI, non-responder imputation; OC, observed case; OLE, open-label extension; PASI, Psoriasis Area and Severity Index; PSO, psoriasis; Q4W, every 4 weeks.

Figure 12: BE ACTIVE and BE ACTIVE 2: MDA, VLDA†, resolution of dactylitis (LDI=0), and resolution of enthesitis (MASES=0) (NRI, OC)



Source: Coates et al, 2022 (174).
Percentages of patients achieving resolution of dactylitis is based on LDI score (includes patients with LDI score >0 at baseline [n=59]).
Percentages of patients achieving resolution of enthesitis is based on the MASES (includes patients with MASES score >0 at baseline [n = 107])
Patients were classified as having MDA or VLDA when they met 5 of 7 or 7 of 7, respectively, of the following criteria: TJC ≤1, SJC ≤1, PASI ≤1 or ≤3% BSA affected by PSO, VAS score ≤15 for pain, VAS score ≤20 for

patient global activity, HAQ-DI ≤0.5, and tender entheseal points score ≤1.
†VLDA is a post-hoc analysis.
Abbreviations: BKZ, bimekizumab; BSA, body surface area; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDI, Leeds Dactylitis Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MDA, minimal disease activity; NRI, non-responder imputation; OC, observed case; PSO, psoriasis; Q4W, every four weeks; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale; VLDA, very low disease activity.

Table 24: BE ACTIVE and BE ACTIVE 2: Efficacy and patient reported outcomes to Week 152 (FAS)††

Week 0–12 (double-blind)		**Any dose BKZ† or placebo →**				**Total BKZ (N=206)**	
Week 12–48 (dose-blind)		**BKZ 160 mg Q4W →**		**BKZ 320 mg Q4W →**			
Week 48–152 (OLE)		**BKZ 160 mg Q4W (n=124)**		**BKZ 160 mg Q4W (n=82)**			
Analysis method		**Imputed‡**	**OC**	**Imputed‡**	**OC**	**Imputed‡**	**OC**
ACR50+ PASI100¶,‡‡ n (%)	Week 48	32 (40.5)	32/72 (44.4)	31 (53.4)	31/55 (56.4)	63 (46.0)	63/127 (49.6)
	Week 96	30 (38.0)	30/65 (46.2)	26 (44.8)	26/49 (53.1)	56 (40.9)	56/114 (49.1)
	Week 152	35 (44.3)	35/61 (57.4)	28 (48.3)	28/45 (62.2)	63 (46.0)	63/106 (59.4)
HAQ-DI mean CFB (SE)	Baseline	1.0 (0.1)		1.0 (0.1)		1.0 (0.04)	
	Week 48	–0.4 (0.1)		–0.5 (0.1)		–0.4 (0.04)	
	Week 96	–0.4 (0.1)		–0.5 (0.1)		–0.5 (0.04)	
	Week 152	–0.4 (0.1)		–0.5 (0.1)		–0.4 (0.04)	
SF-36 PCS mean CFB (SE)	Baseline	37.0 (0.8)		36.0 (1.0)		36.6 (0.6)	
	Week 48	+8.3 (0.8)		+10.3 (1.0)		+9.1 (0.6)	
	Week 96	+8.4 (0.9)		+10.5 (1.1)		+9.2 (0.7)	
	Week 152	+8.7 (0.9)		+9.7 (1.2)		+9.1 (0.7)	
PsARC response‡‡ n (%)	Week 48	92 (74.2)	92/115 (80.0)	69 (84.1)	69/76 (90.8)	161 (78.2)	161/191 (84.3)
	Week 96	84 (67.7)	84/100 (84.0)	66 (80.5)	66/69 (95.7)	150 (72.8)	150/169 (88.8)
	Week 152	80 (64.5)	80/95 (84.2)	60 (73.2)	60/62 (96.8)	140 (68.0)	140/157 (89.2)

Source: Coates et al, 2022 (174); BE ACTIVE and BE ACTIVE 2 TFL data on file (183).
Absolute values at double-blind period baseline presented for continuous endpoints, mean CFB presented beneath.
†At Week 0, patients were randomized to placebo (n=42), BKZ 16 mg Q4W (n=41), BKZ 160 mg Q4W with 320 mg LD (n=41), BKZ 160 mg Q4W (n=41), or BKZ 320 mg Q4W (n=41); ‡NRI data reported for binary endpoints; MI data reported for continuous endpoints; ¶Includes patients with BSA affected by baseline PSO ≥3% (N=137); ††All timepoints are reported relative to baseline (Week 0) of the initial BE ACTIVE study; ‡‡Post-hoc analysis.
Abbreviations: ACR, American College of Rheumatology; BKZ, bimekizumab; BSA, body surface area; CFB, change from baseline; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; MI, multiple imputation; NRI, non-responder imputation; OC, observed case; OLE, open-label extension; PASI,

Psoriasis Area Severity Index; PsARC, psoriatic arthritis response criteria; PSO, psoriasis; Q4W, every 4 weeks; SE, standard error; SF-36 PCS, Short-Form 36 Physical Component Summary.

B.3.7 Subgroup analysis

Not applicable.

B.3.8 Meta-analysis

Not applicable.

B.3.9 Indirect and mixed treatment comparisons

A NMA was conducted using studies identified in the SLR (Section B.3.1) to evaluate the relative efficacy and safety of bimekizumab vs treatments for PsA. The NMA was conducted from the global perspective, and therefore reports on more comparators than are relevant to this submission. Results for bimekizumab 160 mg Q4W vs ixekizumab 80 mg Q4W (the comparator considered most relevant for this submission [Table 1]) are presented in Section B.3.9.4.2 to Section B.3.9.4.4, with results vs all UK licenced comparators presented in Appendix D. Key outcomes of the NMA presented in this submission are ACR20, ACR50, ACR70, PASI75, PASI90, PASI100, PsARC, MDA, HAQ-DI, enthesitis resolution, dactylitis resolution, pain VAS, serious adverse events (SAEs), discontinuation, and discontinuation due to AEs. Other outcomes of interest, presented in Appendix D, include VLDA, FACIT-F, SF-36 MCS, and SF-36 PCS. Other outcomes evaluated are available in the NMA reports submitted in the reference pack (194, 195). Of note, it was not possible to perform NMA analyses of HAQ-DI conditional on PsARC response, due to inadequate published data for the comparators.

B.3.9.1 Summary of analyses performed

For efficacy and HRQoL outcomes, NMA models were conducted across two main populations:

- TNFi-experienced patients
- Patients who are TNFi-CI[a].

Clinical efficacy and HRQoL outcomes in the NMA were considered at Week 16, where data were available (the preferred timepoint). Where no Week 16 data were available, data were considered at Week 12, Week 14 or Week 24. Pre-crossover data were used where possible.

For safety outcomes, the trials were pooled regardless of previous b/tsDMARD exposure as the safety profiles of interventions were not expected to differ between populations (196). Safety

[a] Please see page 19 for a reminder of the population terminology.

analyses included studies where data were available at the preferred timepoint of 16 weeks, or where not available at Week 16 (or if earlier crossover occurred), at Week 12, -14 or -24.

B.3.9.2 Overview of included studies

Studies identified by the SLR (updated January 1st 2023) were assessed for inclusion in the NMA. The criteria for determining study inclusion/exclusion in the NMA is described in Appendix D. In total, 41 studies in either a TNFi-experienced population or b/tsDMARD-naïve population, or in a mixed population were assessed as suitable for inclusion in the NMA. For the network of TNFi-CI patients, the b/tsDMARD-naïve network is used but TNFi treatments are removed based on previous discussions in NICE TA711/TA815 (197, 198). Studies relevant for the comparisons of bimekizumab 160 mg with ixekizumab 80 mg are shown in Table 25, with other studies used for NMAs vs other comparators detailed in Appendix D.

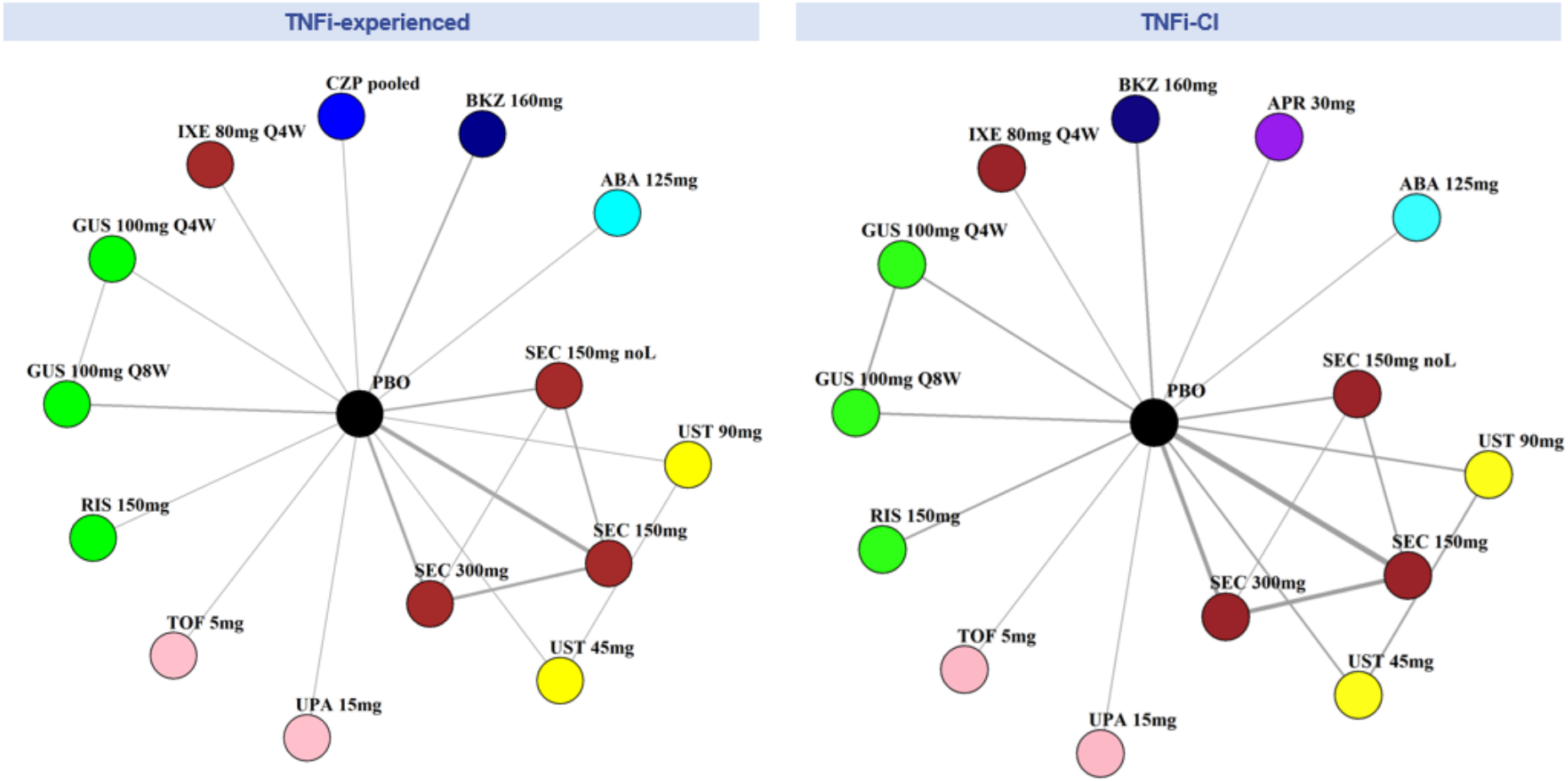
Table 25: List of studies included in the NMAs

Study name	Intervention	TNFi-experienced NMA inclusion	TNFi-CI NMA inclusion
BE ACTIVE	PBO/BKZ	Yes	Yes
BE COMPLETE	PBO/BKZ	Yes	No
BE OPTIMAL	PBO/BKZ/ADA	No	Yes
SPIRIT-P1	PBO/IXE/ADA	No	Yes
SPIRIT-P2	PBO/IXE	Yes	No

Abbreviations: 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.

Example network diagrams for ACR50 (the primary endpoint in the clinical trial programme for bimekizumab) for the TNFi-experienced, and TNFi-CI populations are provided in Figure 13.

Figure 13: ACR50 networks



Abbreviations: ABA, abatacept; ACR, American College of Rheumatology; APR, apremilast; BKZ, bimekizumab; CZP, certolizumab pegol; GUS, guselkumab; IXE, ixekizumab; noL, no loading; PBO, placebo; QXW, every X weeks; RIS, risankizumab; SEC, secukinumab; TNFi, tumour necrosis factor alpha inhibitor; TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab.

B.3.9.3 Methods

B.3.9.3.1 Univariate NMA approach

Analyses consisted of univariate fixed-effect and random-effect Bayesian NMAs on individual binary and continuous outcomes. The analyses further controlled for placebo response using meta-regression (further detail can be found in Appendix D). For all analyses, heterogeneity and inconsistency of the results were assessed using qualitative assessment between inputs and outputs using matrix of OR or mean change as per NICE Decision Support Unit (DSU) technical support document (TSD) 2 (199).

B.3.9.3.2 Model selection and fit

Model fit was explored for adjusted and unadjusted analyses and the best model was selected according to the following rules:

1. Selection between baseline-adjusted vs unadjusted models: if the 95% credible interval (CrI) of baseline risk did not contain zero, baseline-adjusted model was selected; otherwise unadjusted model was selected (NICE TSD 3) (200)

2. Selection between random effects vs fixed effects: if the deviance information criterion (DIC) of random-effects model was lower than the DIC of fixed-effects model by at least three, the random-effects model was selected; otherwise the fixed-effects model was selected (NICE TSD 2) (201).

For QoL outcomes, due to the inherent heterogeneity of the data and the relative consistency of the different QoL versions used between the studies, the random-effects, unadjusted model was selected as the preferred model systematically to address intra-study heterogeneity.

B.3.9.3.3 Programming language

All univariate analyses involved a 10,000 run-in iteration phase and a 10,000-iteration phase for parameter estimation. All calculations were performed using Just Another Gibbs Sampler (JAGS) 3.2.3 (202, 203). Convergence was confirmed through inspection of the ratios of Monte-Carlo error to the SDs of the posteriors; values greater than 5% are strong signs of convergence issues (201).

B.3.9.4 Results

Results of the preferred model (based on the rules outlined in Section B.3.9.3.2) for the univariate NMAs comparing bimekizumab 160 mg Q4W vs ixekizumab 80 mg Q4W (the most relevant comparator for this submission [Table 1]) are presented in Section B.3.9.4.2 for the TNFi-experienced population, Section B.3.9.4.3 for the TNFi-CI population, and Section B.3.9.4.4

for the mixed TNFi-experienced, and b/tsDMARD-naïve population (safety outcomes only). Results vs all UK licenced comparators are presented in Appendix D.

B.3.9.4.1 Model fit statistics

A summary of the model fit statistics for each network (by outcome and population of interest), is presented in Table 26, with full details for the model fit statistics provided in Appendix D.

Table 26: Summary of model fit statistics

	Adjusted				Unadjusted	
	FE		RE		FE	RE
	DIC	Beta (95% CrI)	DIC	Beta (95% CrI)	DIC	DIC
TNFi-experienced patients						
ACR20	260.30	–0.57 (–1.40, 0.07)	259.00	–0.62 (–1.60, 0.13)	273.07	**252.58**
ACR50	213.56	–1.40 (–3.63, 1.78)	207.25	–1.76 (–3.95, 0.43)	261.98	**205.33**
ACR70	**163.10**	**–1.08 (–2.40, –0.45)**	165.93	–1.09 (–1.90, –0.58)	253.32	161.51
PASI75	142.67	–1.63 (–4.03, 2.28)	144.05	**–**1.04 (–5.75, 3.21)	149.27	**144.25**
PASI90	110.95	–0.89 (–2.91, 15.36)	109.85	–1.01 (–2.29, 2.71)	**114.55**	111.92
PASI100	79.90	–0.74 (–0.98, 0.88)	79.35	–0.84 (–1.17, 3.04)	87.50	**81.76**
PsARC	94.84	–10.96 (–18.47, 1.15)	97.09	7.73 (2.34, 19.17)	**97.32**	96.65
MDA	122.20	–1.10 (–6.09, 1.32)	123.99	–0.57 (–2.07, 1.04)	156.25	**123.69**
HAQ-DI	–64.63	–1.31 (–12.62, 3.31)	–63.35	–1.11 (–6.85, 2.63)	–63.95	**–62.12**
Enthesitis	91.35	13.59 (–23.00, 46.01)	93.40	–3.55 (–25.78, 11.74)	**94.06**	91.55
Dactylitis	66.36	2.48 (–0.46, 22.35)	67.96	0.35 (–25.52, 12.42)	**65.64**	65.88
Pain VAS	79.11	3.33 (–13.70, 28.51)	76.58	3.42 (–3.58, 23.27)	79.96	**78.21**
TNFi-CI patients						
ACR20	343.69	–0.33 (–0.65, 0.23)	343.36	–0.48 (–1.14, 0.11)	392.29	**338.79**
ACR50	303.66	–0.32 (–0.66, 0.47)	303.20	–0.44 (–1.41, 0.83)	493.89	**294.22**
ACR70	**236.58**	**–0.76 (–0.92, –0.50)**	235.21	–0.78 (–0.99, –0.50)	633.89	237.77
PASI75	83.41	0.13 (–5.23, 16.85)	82.56	–0.46 (–5.03, 7.41)	**84.62**	81.82
PASI90	153.07	–1.29 (–2.22, 0.79)	150.77	–1.02 (–3.00, 4.12)	168.03	**153.02**

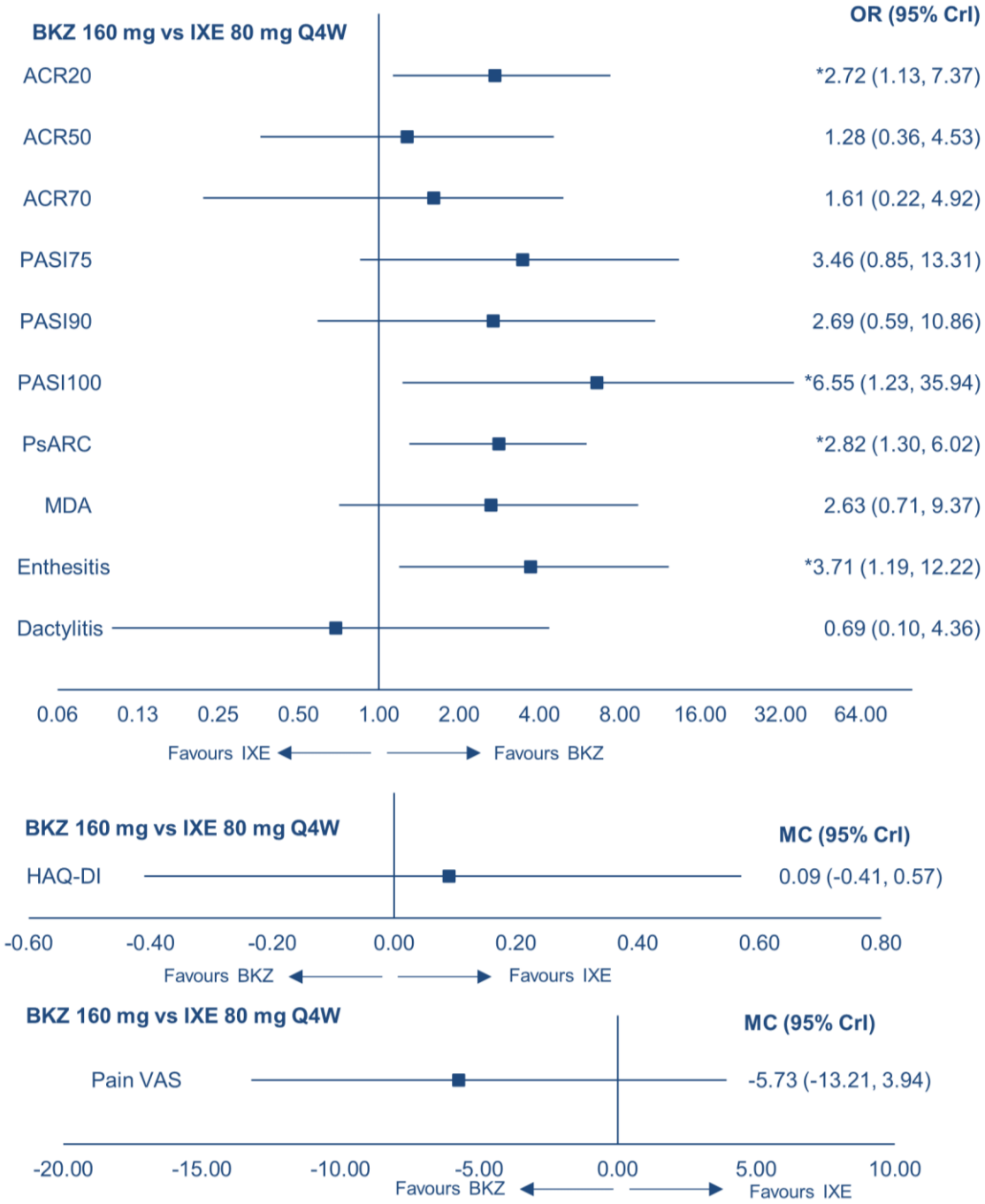
	Adjusted				Unadjusted	
	FE		RE		FE	RE
	DIC	Beta (95% CrI)	DIC	Beta (95% CrI)	DIC	DIC
PASI100†	97.18	–1.05 (–1.89, 0.18)	**96.97**	**–1.07 (–2.31, –0.33)**	114.83	98.10
PsARC	132.69	–0.45 (–3.50, 4.03)	133.88	–0.54 (–2.62, 3.47)	**134.81**	132.82
Mixed population of patients who are b/tsDMARD-naïve or TNFi-experienced						
SAE	**480.52**	**–0.75 (–1.14, –0.38)**	489.44	–0.84 (–1.23, –0.49)	4524.11	465.12
Discontinuation	**399.90**	**–0.44 (–0.71, –0.13)**	408.32	–0.50 (–0.83, –0.09)	1913.65	401.60
Discontinuation due to AEs	**438.38**	**–0.79 (–1.01, –0.52)**	439.55	–0.82 (–1.03, –0.52)	5005.54	428.94

Source: Efficacy and safety outcomes 2023 NMA report (194), HRQoL and extra-articular manifestations 2023 NMA report (195), UCB data on file 2023 (204), and UCB data on file 2023 (205).
The preferred model is in bold.
†The RE adjusted was selected as the best fitting model, as although it did not meet the criteria of a 3-point benefit over the FE adjusted model, the decision rule would have then selected the RE unadjusted model, and the adjusted model fit is better.
Abbreviations: ACR, American College of Rheumatology; AE, adverse event; b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; CrI, credible interval; DIC, deviance information criterion; FE, fixed effects; HAQ-DI, Health-assessment questionnaire-disability index; MDA, minimal disease activity; PASI, psoriasis area and severity index; PsARC, psoriatic arthritis response criteria; RE, random effects; SAE, serious adverse event; TNFi, tumour necrosis factor alpha inhibitor; TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated; VAS, visual analogue scale.

B.3.9.4.2 Efficacy outcomes in the TNFi-experienced population

Using the preferred model for each outcome (Table 26), in patients with PsA who are TNFi-experienced, bimekizumab 160 mg was statistically superior vs ixekizumab 80 mg Q4W for ACR20, PASI100, PsARC, and enthesitis resolution (according to LEI). There was no statistically significant difference between bimekizumab 160 mg and ixekizumab 80 mg Q4W for the other key efficacy and HRQoL outcomes, including ACR50, ACR70, PASI75, PASI90, MDA response, dactylitis resolution (according to LDI), HAQ-DI, and pain VAS (Figure 14).

Figure 14: Forest plot for key efficacy outcomes – TNFi-experienced population

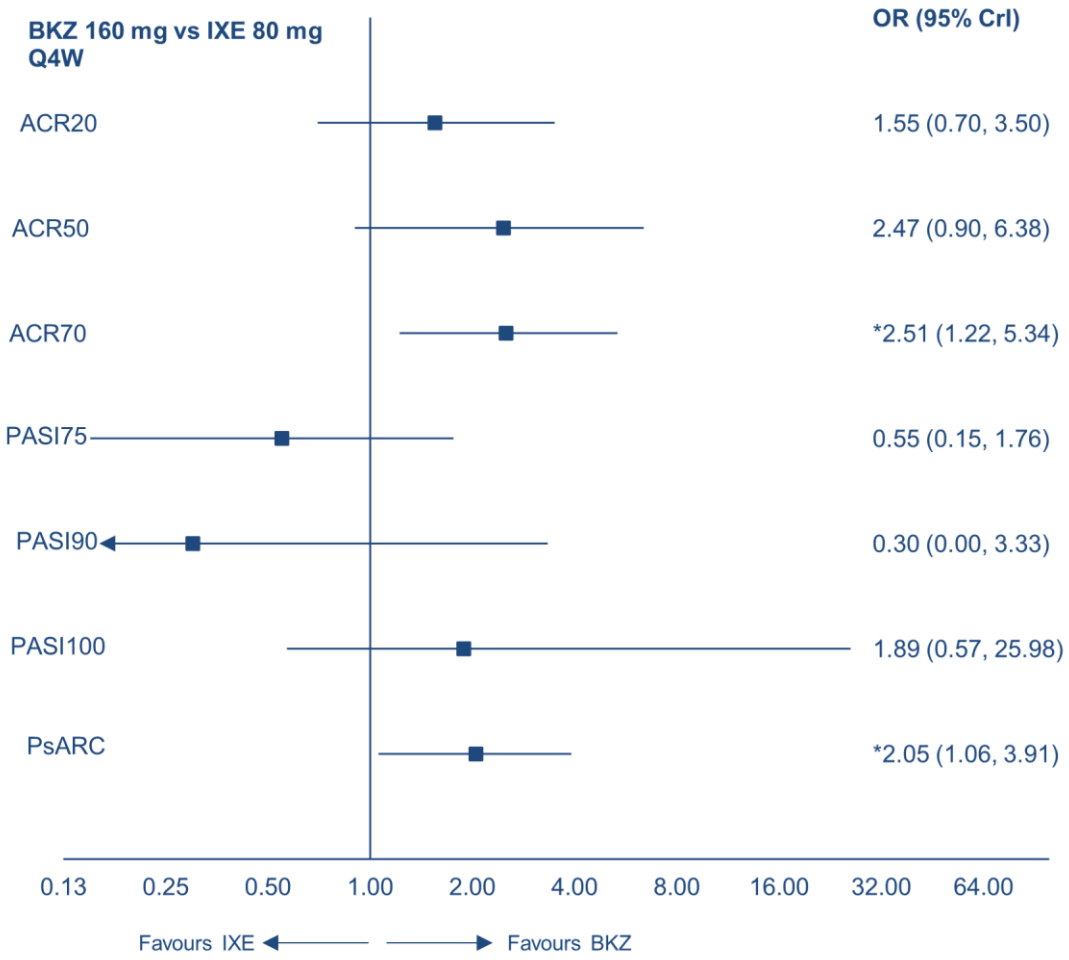


Source: Efficacy and safety outcomes NMA report 2023 NMA report (194), HRQoL and extra-articular manifestations 2023 NMA report (195).
The preferred model for each outcome is presented. The RE unadjusted model is presented for ACR20, ACR50, PASI75, PASI100, MDA, HAQ-DI, and pain VAS, and the FE unadjusted for PASI90, PsARC, enthesitis resolution, and dactylitis resolution, and the FE adjusted for ACR70.
*Indicates a statistically significant difference.
Abbreviations: ACR, American College of Rheumatology; BKZ, bimekizumab; CrI, credible interval; FE, fixed effects; HAQ-DI, health assessment questionnaire-disability index; IXE, ixekizumab; MC, mean change; MDA, minimal disease activity; NMA, network meta-analysis; OR, odds ratio; PASI, psoriasis area and severity index; PsARC, psoriatic arthritis response criteria; Q4W, every 4 weeks; RE, random effects; TNFi, tumour necrosis factor alpha-inhibitor; VAS, visual analogue scale.

B.3.9.4.3 Efficacy outcomes in the TNFi-CI population

Using the preferred model for each outcome (Table 26), in patients with PsA who are TNFi-CI, bimekizumab 160 mg was statistically superior vs ixekizumab for ACR70, and PsARC, with no significant difference for ACR20, ACR50, PASI75, PASI90, and PASI100 (Figure 15).

Figure 15: Forest plot for key efficacy outcomes – TNFi-CI population



Source: UCB data on file (204).
The preferred model is presented for each outcome. The unadjusted RE is presented for ACR20, ACR50, and PASI90, the adjusted FE for ACR70, the adjusted RE for PASI100, and the unadjusted FE for PASI75, and PsARC.
*Indicates a statistically significant difference.
Abbreviations: ACR, American College of Rheumatology; BKZ, bimekizumab; CrI, credible interval; FE, fixed effects; IXE, ixekizumab; OR, odds ratio; PASI, psoriasis area and severity index; PsARC, psoriatic arthritis response criteria; Q4W, every 4 weeks; RE, random effects; TNFi-CI, tumour necrosis factor alpha inhibitor contraindicated.

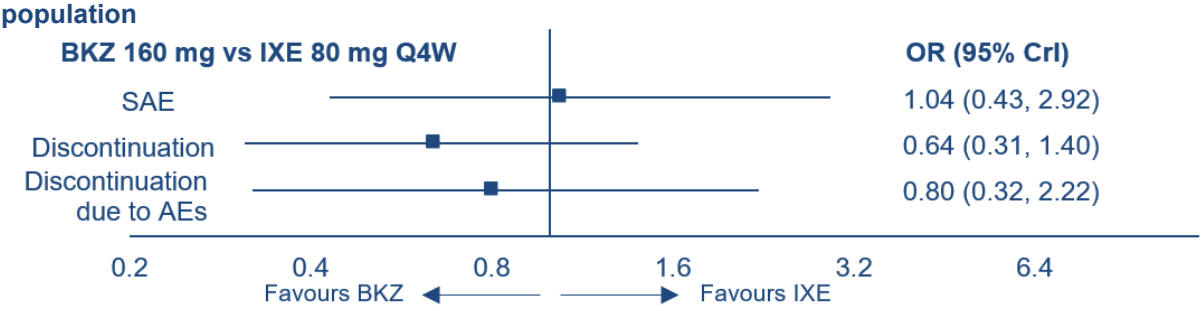
B.3.9.4.4 Safety outcomes in pooled b/tsDMARD-naïve and TNFi-experienced patients

B.3.9.4.4.1 SAEs, discontinuation, and discontinuation due to AEs

Using the FE adjusted model, there was no significant difference between bimekizumab and ixekizumab for SAEs, discontinuation, and discontinuation due to AEs (Figure 16).

Notably, all of the safety NMAs are based on a small number of SAEs, discontinuations, and discontinuations due to AEs. At 12–24 weeks, in total, 1 patient receiving bimekizumab in BE ACTIVE reported SAEs, discontinuation, or discontinuation due to AEs, each, while 5, 4, and 2 patients from BE COMPLETE, and 7, 16, and 8 patients from BE OPTIMAL reported these events, respectively. In total, 10, 21, and 7 patients receiving ixekizumab 80 mg Q4W in SPIRIT-H2H, 6, 10, and 2 in SPIRIT-P1, and 3, 11, and 5 in SPIRIT-P2 reported SAEs, discontinuation, or discontinuation due to AEs, respectively.

Figure 16. Forest plot for SAEs, discontinuation, and discontinuations due to AEs – mixed population



Source: UCB data on file (205).
The results are presented for the FE adjusted model.
The scaling on the x axis is a log scale.
Abbreviations: AE, adverse event; BKZ, bimekizumab; CrI, credible interval; FE, fixed effect; IXE, ixekizumab; OR, odds ratio; Q4W, every 4 weeks; SAE, serious adverse event.

B.3.9.5 Subgroup analysis

N/A.

B.3.9.6 Uncertainties in the indirect and mixed treatment comparisons

Due to a low number of events, no model would converge for serious infections, and an NMA was not possible, therefore the rates of serious infections are presented in Appendix D.

Despite applying robust methodologies, the analyses had some inherent limitations. Relatively few studies were identified for ixekizumab (three in total), resulting in sparse networks for some less well-reported outcomes, especially in the TNFi-experienced population. This may have reduced the confidence of the estimates and limited the ability to assess consistency within networks.

The trials included showed some degree of heterogeneity in population (prior cDMARD use) and other characteristics such as age, sex, baseline disease severity, and concomitant medication use (Appendix D). Areas of potential heterogeneity were reviewed to ensure all studies could be fairly compared (196). In addition, four model types were conducted for each outcome, using both fixed and random effects as well as being unadjusted and adjusted for baseline (placebo) risk. Comparing these models and selecting the best-fitting model should minimise the bias introduced by study heterogeneity.

Not all trials reported outcomes at the same timepoint, which could lead to lack of comparability of trial results. Some trials utilised an early escape and crossover design. In BE ACTIVE and BE COMPLETE, patients were re-randomised to bimekizumab at Week 12 and Week 16, respectively; in BE OPTIMAL, placebo crossover to bimekizumab occurred at Week 16; in SPIRIT-P2 early escape was permitted at Week 16, and placebo cross over occurred at Week 24; in SPIRIT-P1 early escape was permitted at Week 16; and in SPIRIT-H2H no crossover occurred. This potentially introduced bias into analysis of intention-to-treat population results (especially in the case of crossover), however use of pre-crossover data mitigated the issue. In addition, where outcomes were reported at different timepoints, the timepoints closest to the primary outcomes in the bimekizumab trials (16 weeks) were selected in order to minimise bias.

In some cases, trials reported no patients reporting certain outcomes in one or more arms. A correction was applied to try to mitigate the issue, whereby a patient with an event was added to each arm of the trial. Without the correction, most models were not convergent or were providing large posterior distribution making little clinical sense (25).

Finally, safety results were associated with some uncertainty due to the low number of events, as all treatments presented a relatively safe profile.

B.3.9.7 Strengths of the analysis

This analysis provides an up-to-date synthesis of available evidence for several efficacy and safety outcomes for bimekizumab and ixekizumab, with comparison possible between bimekizumab and ixekizumab where this was not available from head-to-head trials (and other therapeutic regimens used in clinical practice presented in Appendix D). All NMAs were conducted per the recommendations from the NICE DSU specification (201), in close collaboration with clinical experts. The NMAs followed strict inclusion and exclusion criteria, based on previous health technology appraisals (HTA) (75, 78, 79, 147-152, 171), with a transparent selection of models. The NMA results were consistent across the two separate patient populations (TNFi-experienced, and TNFi-CI); these populations are in line with the decision problem populations.

B.3.10 Adverse reactions

B.3.10.1 Primary evidence

B.3.10.1.1 BE COMPLETE

B.3.10.1.1.1 Overall summary of TEAEs

During BE COMPLETE, in a TNFi-IR population[a], the total duration of exposure was higher in the bimekizumab arm vs the placebo arm (81.0 patient years [PY] vs 39.5 PY), as expected, based on the 2:1 randomisation.

In total, 108 (40%) patients reported treatment-emergent adverse events (TEAE) in the bimekizumab arm, vs 44 (33%) patients in the placebo arm (Table 27). The incidence of drug-related TEAEs was higher in the bimekizumab arm, with 35 (13%) patients reporting treatment-related TEAEs vs 4 (3%) patients in the placebo arm. The proportion of patients with serious TEAEs were low, occurring in 5 (2%) patients in the bimekizumab arm and no patients in the placebo arm. No serious TEAEs were considered to be related to bimekizumab by the investigator. None of the serious or severe TEAEs led to discontinuation. Two (1%) patients receiving bimekizumab reported TEAEs leading to study discontinuation (one case of stomatitis, and one of oral candidiasis). Both TEAEs were moderate in intensity and had recovered or resolved (oral candidiasis was considered to be related to treatment by the investigator, while stomatitis was not). No deaths were reported during the study.

[a] Please see page 19 for a reminder of the population terminology.

TEAE incidence was corrected for duration of exposure, and the resulting incidence rate (i.e. new cases per 100 PY) was 167.2/100 PY in the bimekizumab arm, and 127.3/100 PY in the placebo arm. Of the most commonly reported TEAEs (≥2% in any treatment arm) by preferred term, the incidences were numerically higher in the bimekizumab arm vs the placebo group for oral candidiasis (7 [3%] vs 0 patients, respectively), nasopharyngitis (10 [4%] vs 1 patient [1%], respectively), and upper respiratory tract infection (6 patients [2%] vs 2 patients [2%], respectively).

Table 27: BE COMPLETE: Summary of TEAEs (SS)

N (%)	PBO N=132	BKZ 160 mg Q4W N=267
Any TEAE	44 (33)	108 (40)
Serious TEAEs†	0	5 (2)
TEAEs of safety topic of interest	2 (1.5)	23 (8.6)
TEAEs leading to study discontinuation‡	0	2 (1)
Drug-related TEAEs	4 (3)	35 (13)
Severe TEAEs¶	0	5 (2)
Deaths	0	0
Incidence and incidence rate of TEAEs occurring in ≥2% of patients		
Oral candidiasis	0	7 (3)
Nasopharyngitis	1 (1)	10 (4)
Upper RTI	2 (2)	6 (2)
Urinary tract infection	3 (2)	5 (2)
Coronavirus infection	6 (5)	5 (2)
Hypertension	3 (2)	3 (1)

Source: Merola et al, 2023 (172) and BE COMPLETE Week 16 CSR (175).
Note: n=number of patients who reported at least 1 TEAE in that category.
†One case of intestinal obstruction, one of bronchitis, one of COVID-19 pneumonia, one of joint injury, and one of toxic encephalopathy; ‡One case of stomatitis and one of oral candidiasis; ¶Six events in five patients: one case of bronchitis, one of back pain, one of toxic encephalopathy, one of headache, one of pruritis, and one of renal pain; one patient reported both severe back pain and renal pain.
Abbreviations: BKZ, bimekizumab; PBO, placebo; Q4W, every 4 weeks; RTI, respiratory tract infection; SS, safety set; TEAE, treatment-emergent adverse event.

B.3.10.1.1.2 Safety topics of interest

Serious infections were reported in 2 (1%) patients in the bimekizumab arm (one case each of bronchitis, and COVID-19). No opportunistic infections, or cases of active tuberculosis were reported during the study. Fungal infections were reported in 12 (4%) patients receiving bimekizumab vs no patients receiving placebo. Of the fungal infections, 7 (3%) patients had *Candida* infections, all of which were oral candidiasis (one patient had recurrent infection, which did not lead to study discontinuation). All fungal infections were mild or moderate and none were systemic. One moderate *Candida* infection led to study discontinuation. There was one malignancy (basal cell carcinoma in the placebo group) and no reported cases of major adverse cardiovascular events (MACE), uveitis, IBD, or suicidal ideation and behaviour. The incidence of

injection site reactions was low, reported by 3 (1%) patients in the bimekizumab group and none in the placebo group. Four (1%) patients receiving bimekizumab reported neutropenia, all of which were non-serious and did not lead to study discontinuation. Hepatic events were reported in 8 (3%) patients receiving bimekizumab and 2 (2%) patients receiving placebo; most of these were increased liver enzyme concentrations and none led to discontinuation.

B.3.10.1.2 BE OPTIMAL

B.3.10.1.2.1 Overall summary of TEAEs

In BE OPTIMAL, in bDMARD-naïve patients[a], during the double-blind treatment period (Weeks 1 to 16), the duration of treatment exposure was higher in the bimekizumab arm vs the placebo and adalimumab arms (130.1 PY vs 83.8 PY vs 42.2 PY, respectively), as expected based on the 3:2:1 randomisation scheme. During the overall study period the duration of treatment exposure for bimekizumab (including patients randomised to bimekizumab, and patients who switched from placebo at Week 16) was 583.3 PY vs 130.5 PY for the adalimumab group.

During the double-blind treatment period (Weeks 0–16), the incidence of TEAEs was higher in the bimekizumab 160 mg Q4W group (60%) than the placebo group (49%) (Table 28). By Week 16, 59% of patients receiving adalimumab had at least one TEAE. During the overall study period (Weeks 0–52), TEAEs were reported by 555 (79%) patients in the bimekizumab 160 mg Q4W group, and 113 (81%) in the adalimumab group. The incidence of serious TEAEs was low overall across all treatment groups, recorded for eight (2%) patients receiving bimekizumab, three (1%) receiving placebo, and two (1%) receiving adalimumab. Discontinuations due to TEAEs were low (bimekizumab: 8 [2%]; placebo: 3 [1%]; adalimumab: 3 [2%]).

To Week 52, serious TEAEs were reported for 46 (7%) patients receiving bimekizumab, and 10 (7%) receiving adalimumab. The majority of serious TEAEs were assessed as not related to the IMP by the investigator, were considered recovering or resolved, and did not lead to study discontinuation. Discontinuations due to TEAEs up to and including Week 52 were low (bimekizumab: 21 [3%]; adalimumab: 7 [5%]). No deaths were reported in any of the treatment groups during the study, except for one patient in the bimekizumab group, who had a TEAE (motorcycle accident) that led to death during the overall study period.

At Week 52, the most commonly reported TEAEs in the bimekizumab arm were nasopharyngitis (84 [12%]), upper respiratory tract infection (50 [7%]), urinary tract infection (43 [6%]), headache (41 [6%]), oral candidiasis (38 [5%]), and diarrhoea (36 [5%]).

[a] Please see page 19 for a reminder of the population terminology.

During the overall study period, 5 (0.7%) patients receiving bimekizumab and 2 (1.4%) in the adalimumab group reported serious TEAEs considered related to the IMP by the investigator.

Table 28: BE OPTIMAL: Safety summary

n (%)	Double-blind period (Weeks 0–16) (SS)			Overall (Weeks 0–52) (AMS)	
	PBO N=281	BKZ 160 mg Q4W N=431	ADA 40 mg Q2W reference arm‡ N=140	BKZ 160 mg Q4W Total† N=702	ADA 40 mg Q2W reference arm‡ N=140
Overall summary of TEAEs					
Any TEAE	139 (49)	257 (60)	83 (59)	555 (79)	113 (81)
Serious TEAEs	3 (1)	8 (2)	2 (1)	46 (7)	10 (7)
TEAEs of safety topic of interest	23 (8)	64 (15)	20 (14)	217 (31)	43 (31)
Discontinuation due to TEAEs	3 (1)	8 (2)	3 (2)	21 (3)	7 (5)
Drug-related TEAEs	35 (12)	100 (23)	34 (24)	224 (32)	54 (39)
Severe TEAEs	0	4 (1)	3 (2)	23 (3)	9 (6)
Death	0	0	0	1 (0.1)¶	0
Incidence and incidence rate of most frequently reported TEAEs (≥5% of patients in any treatment group in any period)					
Nasopharyngitis	13 (5)	40 (9)	7 (5)	84 (12)	12 (8.6)
Upper RTI	18 (6)	22 (5)	3 (2)	50 (7)	8 (6)
Urinary tract infection	4 (1)	9 (2)	3 (2)	43 (6)	5 (4)
Headache	7 (2)	19 (4)	2 (1)	41 (6)	6 (4)
Oral candidiasis	0	9 (2)	0	38 (5)	1 (1)
Diarrhoea	7 (2)	16 (4)	5 (4)	36 (5)	7 (5)
Hypertension	11 (4)	12 (3)	4 (3)	29 (4)	9 (6)
ALT elevation	2 (1)	3 (1)	7 (5)	16 (2)	11 (8)
AST elevation	2 (1)	1 (<1)	4 (3)	14 (2)	7 (5)
Injection site erythema	0	1 (<1)	4 (3)	6 (1)	7 (5.0)

Source: McInnes et al, 2023 (55), BE OPTIMAL Week 52 CSR (178), and Ritchlin et al, 2022 (179).
n=number of patients who reported at least 1 TEAE in that category.
†Includes patients who switched from PBO to BKZ (events after switch only); ‡The adalimumab reference arm was not powered for statistical comparisons vs bimekizumab or placebo; ¶Motorcycle accident.
Abbreviations: ADA, adalimumab; ALT, alanine aminotransferase; AMS, Active Medication Set; AST, aspartate aminotransferase; BKZ, bimekizumab; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RTI, respiratory tract infection; SS, safety set; TEAE, treatment-emergent adverse event.

B.3.10.1.2.2 Safety topics of interest

To Week 16, there was one serious infection in each of the bimekizumab (pneumonia) and adalimumab (herpes zoster) arms, and none with placebo. To Week 52, 6 (0.9%) of patients receiving bimekizumab (including those randomly assigned and those who switched from placebo at Week 16) experienced serious infections, the majority of which were mild or moderate in intensity and not considered related to the IMP. To Week 52, one patient in the adalimumab group experienced two serious infections. At Week 16, no patients receiving bimekizumab, or

placebo had an opportunistic infection. One (1%) patient in the adalimumab arm reported an opportunistic infection. To Week 52, 9 (1%) patients receiving bimekizumab had opportunistic infections. The herpes zoster SAE was the only opportunistic event in the adalimumab group to Week 52. The majority of opportunistic infection TEAEs were assessed as related to IMP by the Investigator, all recovered or resolved, and none led to study discontinuation. No cases of active tuberculosis (TB) were reported during the study.

By Week 16, 20 (5%) patients receiving bimekizumab had a fungal infection; 11 (3%) were reported as *Candida* infections. Four (1%) patients had a fungal infection while receiving placebo, two (1%) of which were reported specifically as vulvovaginal candidiasis and the others as vulvovaginal mycotic infections. By Week 52, 82 (11.7%) patients assigned to bimekizumab had a fungal infection and 54 (7.7%) were reported as *Candida* infections; the majority (38 [5.4%] patients) were oral candidiasis. By Week 52, 29 (4.1%) patients assigned to bimekizumab had fungal infections not elsewhere classified. The majority of fungal infections with bimekizumab were mild or moderate in severity, were not serious, and recovered or resolved. Only two patients reported fungal infections that led to study discontinuation (oral candidiasis, and tongue fungal infection). By Week 52, 2 (1.4%) patients had a fungal infection in the adalimumab group, 1 (0.7%) was reported as candida infection, and 1 (0.7%) as tinea infections.

Two malignancies occurred by Week 16, one (<1%) in a patient receiving bimekizumab (basal cell carcinoma) and one (<1%) in a patient receiving placebo (breast cancer Stage I, which led to study discontinuation). Overall, the incidence of malignance TEAEs was low to Week 52, reported in 7 (1.0%) patients receiving bimekizumab. All malignancy TEAEs recovered or resolved and did not lead to study discontinuation, except for colon cancer (assessed as not drug-related), and chronic lymphocytic leukaemia Stage 0 (assessed as drug-related and led to study discontinuation). No patients reported malignancy TEAEs in the adalimumab group.

Four adjudicated MACE were recorded in the bimekizumab group to Week 52; these were not deemed to be drug-related. No adjudicated MACE occurred in the adalimumab group. During the overall study period, 2 (0.3%) patients were adjudicated as having definite IBD, and 2 (0.3%) probable IBD. No patients in the adalimumab group had IBD TEAEs referred to the Adjudication Committee.

By Week 52, 16 (2.3%) patients in the bimekizumab group, and 11 (7.9%) patients in the adalimumab group had alanine aminotransferase levels of ≥3x upper limit of normal (ULN). Furthermore, 14 (2.0%) patients in the bimekizumab group, and 7 (5.0%) patients in the adalimumab group had aspartate aminotransferase levels of ≥3x ULN. The majority of patients with liver enzyme elevations had confounding risk factors (i.e. concomitant MTX), and elevations were transient and recovered during the study and did not lead to study discontinuation.

No cases of suicidal ideation and behaviour were reported during the study in any arm. During the overall study period, the incidences of neutropenia and injection site reactions were low with bimekizumab and adalimumab (neutropenia: 11 (1.6%) patients and 2 (1%), respectively; injection site reaction: 15 (2.1%) patients and 13 (9.1%) patients, respectively).

B.3.10.2 Supporting evidence

B.3.10.2.1 BE ACTIVE and BE ACTIVE 2

A summary of safety results for total exposure to bimekizumab across the Phase 2 study BE ACTIVE (Weeks 0–48), the OLE extension study BE ACTIVE 2 (Weeks 48–152) and the BE ACTIVE + OLE (Weeks 0–152) is presented in Table 29. Over these periods, the safety profile of bimekizumab was consistent with previous reports, with no new safety signals identified.

Table 29: BE ACTIVE and BE ACTIVE 2: Safety summary (SS)

Trial	BE ACTIVE		BE ACTIVE 2	BE ACTIVE + OLE
n (%) [EAIR/100 PY]	Weeks 0–48[†,‡]		Weeks 48–152	Weeks 0–152[¶]
	BKZ 160 mg Q4W (n=126; 113.2 PY)[§]	BKZ 320 mg Q4W (n=80; 72.9 PY)[§]	Total BKZ (N=183; 392.7 PY)	Total BKZ (N=206; 570.1 PY)
Any TEAE	94 (74.6) [177.6]	57 (71.3) [165.9]	148 (80.9) [94.3]	184 (89.3) [126.4]
Serious TEAEs	8 (6.3) [7.9]	0	14 (7.7) [3.8]	22 (10.7) [4.1]
Severe TEAEs	5 (4.0) [4.6]	2 (2.5) [2.9]	8 (4.4) [2.1]	14 (6.8) [2.5]
Withdrawal due to TEAEs	6 (4.8) [5.9]	2 (2.5) [3.1]	9 (4.9) [2.3]	17 (8.3) [3.0]
Drug-related TEAEs	43 (34.1) [52.7]	29 (36.3) [57.0]	60 (32.8) [20.0]	97 (47.1) [26.4]
Deaths	0	0	0	0
Most frequently reported TEAEs (≥5%) by MedDRA preferred term				
Nasopharyngitis	12 (9.5) [12.0]	11 (13.8) [18.4]	19 (10.4) [5.2]	37 (18.0) [7.6]
Upper respiratory tract infection	12 (9.5) [12.0]	8 (10.0) [13.2]	20 (10.9) [5.5]	34 (16.5) [6.8]
Bronchitis	7 (5.6) [6.9]	3 (3.8) [4.8]	11 (6.0) [2.9]	19 (9.2) [3.5]
Oral candidiasis[††]	6 (4.8) [6.0]	4 (5.0) [6.4]	13 (7.1) [3.5]	19 (9.2) [3.5]
Pharyngitis	4 (3.2) [3.9]	7 (8.8) [11.6]	10 (5.5) [2.7]	17 (8.3) [3.2]
Sinusitis	6 (4.8) [5.9]	4 (5.0) [6.5]	10 (5.5) [2.6]	17 (8.3) [3.2]
Psoriasis	2 (1.6) [1.9]	2 (2.5) [3.1]	14 (7.7) [3.7]	16 (7.8) [2.9]
Psoriatic arthropathy	2 (1.6) [1.9]	1 (1.3) [1.6]	12 (6.6) [3.1]	16 (7.8) [2.9]
Respiratory tract infection	8 (6.3) [8.0]	2 (2.5) [3.2]	4 (2.2) [1.0]	15 (7.3) [2.8]
Oral fungal infection	3 (2.4) [2.9]	3 (3.8) [4.7]	9 (4.9) [2.4]	14 (6.8) [2.6]
Tonsillitis	6 (4.8) [5.9]	2 (2.5) [3.2]	6 (3.3) [1.6]	14 (6.8) [2.6]
ALT increased	6 (4.8) [6.0]	3 (3.8) [4.7]	6 (3.3) [1.6]	13 (6.3) [2.4]

Trial	BE ACTIVE		BE ACTIVE 2	BE ACTIVE + OLE
n (%) [EAIR/100 PY]	Weeks 0–48[†,‡]		Weeks 48–152	Weeks 0–152[¶]
	BKZ 160 mg Q4W (n=126; 113.2 PY)[§]	BKZ 320 mg Q4W (n=80; 72.9 PY)[§]	Total BKZ (N=183; 392.7 PY)	Total BKZ (N=206; 570.1 PY)
Safety topics of interest				
Serious infections	3 (2.4) [2.9]	0	1 (0.5) [0.3]	4 (1.9) [0.7]
Fungal infections[‡‡]	17 (13.5) [17.8]	10 (12.5) [16.7]	32 (17.5) [9.2]	47 (22.8) [9.7]
Candida infections	9 (7.1) [9.1]	5 (6.3) [8.1]	16 (8.7) [4.3]	24 (11.7) [4.6]
Oral candidiasis[††]	6 (4.8) [6.0]	4 (5.0) [6.4]	13 (7.1) [3.5]	19 (9.2) [3.5]
Skin candidiasis	1 (0.8) [1.0]	0	1 (0.5) [0.3]	2 (1.0) [0.4]
Vulvovaginal candidiasis	0	0	1 (0.5) [0.3]	1 (0.5) [0.2]
Genital candidiasis	1 (0.8) [1.0]	0	1 (0.5) [0.3]	1 (0.5) [0.2]
Oropharyngeal candidiasis	1 (0.8) [1.0]	0	0	1 (0.5) [0.2]
Fungal infections NEC	9 (7.1) [9.0]	4 (5.0) [6.3]	17 (9.3) [4.6]	25 (12.1) [4.7]
Oral fungal infection	3 (2.4) [2.9]	3 (3.8) [4.7]	9 (4.9) [2.4]	14 (6.8) [2.6]
Tongue fungal infection	3 (2.4) [2.9]	0	4 (2.2) [1.0]	5 (2.4) [0.9]
Fungal skin infection	0	1 (1.3) [1.6]	3 (1.6) [0.8]	4 (1.9) [0.7]
Fungal esophagitis	1 (0.8) [1.0]	1 (1.3) [1.6]	1 (0.5) [0.3]	3 (1.5) [0.5]
Vulvovaginal mycotic infection	2 (1.6) [1.9]	0	0	2 (1.0) [0.4]
Onychomycosis	0	0	2 (1.1) [0.5]	2 (1.0) [0.4]
Fungal pharyngitis	0	0	1 (0.5) [0.3]	1 (0.5) [0.2]
Tinea infections	0	1 (1.3) [1.6]	1 (0.5) [0.3]	2 (1.0) [0.4]
Tinea pedis	0	1 (1.3) [1.6]	0	1 (0.5) [0.2]
Tineas cruris	0	0	1 (0.5) [0.3]	1 (0.5) [0.2]
Serious hypersensitivity reactions	0	0	0	0
Opportunistic infections[¶¶]	1 (0.8) [1.0]	1 (1.3) [1.6]	1 (0.5) [0.3]	3 (1.5) [0.5]
Active tuberculosis	0	0	0	0
Liver enzyme elevation[§§]				
ALT increased	6 (4.8) [6.0]	3 (3.8) [4.7]	6 (3.3) [1.6]	13 (6.3) [2.4]
AST increased	4 (3.2) [4.0]	2 (2.5) [3.1]	6 (3.3) [1.6]	10 (4.9) [1.8]
Hepatic enzymes increased	2 (1.6) [1.9]	1 (1.3) [1.6]	1 (0.5) [0.3]	4 (1.9) [0.7]
MACE[†††]	0	0	0	0
Malignancies[‡‡‡]	1 (0.8) [1.0]	0	0	1 (0.5) [0.2]
IBD[†††]	0	0	1 (0.5) [0.3]	1 (0.5) [0.2]
Microscopic colitis	0	0	1 (0.5) [0.3]	1 (0.5) [0.2]

Trial	BE ACTIVE		BE ACTIVE 2	BE ACTIVE + OLE
n (%) [EAIR/100 PY]	Weeks 0–48[†,‡]		Weeks 48–152	Weeks 0–152[¶]
	BKZ 160 mg Q4W (n=126; 113.2 PY)[§]	BKZ 320 mg Q4W (n=80; 72.9 PY)[§]	Total BKZ (N=183; 392.7 PY)	Total BKZ (N=206; 570.1 PY)
Anterior uveitis	0	0	0	0
Neutropenia	0	1 (1.3) [1.6]	5 (2.7) [1.3]	6 (2.9) [1.1]
Drug hypersensitivity[¶¶¶]	2 (1.6) [1.9]	0	1 (0.5) [0.3]	3 (1.5) [0.5]
Injection site reactions	0	3 (3.8) [4.9]	0	3 (1.5) [0.5]
SIB[†††]	1 (0.8) [1.0]	0	0	1 (0.5) [0.2]
Depression	1 (0.8) [1.0]	1 (1.3) [1.6]	2 (1.1) [0.5]	4 (1.9) [0.7]

Source: Coates et al, 2022 (174) and Coates et al, 2021 (206).
After Week 48, all patients received BKZ 160 mg Q4W, regardless of prior dosing regimen.
†Includes patients re-randomised 1:1 at Week 12 from PBO or BKZ 16 mg Q4W to BKZ 160 mg Q4W or BKZ 320 mg Q4W; ‡Two patients completing the double-blind period on placebo were re-randomised but did not receive BKZ; ¶Includes safety follow-up to possible 168 weeks total for some patients; §Two patients included in both groups due to a dosing error, allocation done per actual treatment; ††All oral candidiasis TEAEs were mild to moderate (no serious cases); ‡‡All fungal infections were mild to moderate and localized, not systemic; ¶¶Two patients reported three opportunistic events (two fungal esophagitis, one oropharyngeal candidiasis) in Weeks 0–48, one patient reported two events (fungal pharyngitis, fungal esophagitis) in Weeks 48–152; §§No Hy's law cases reported; †††Events adjudicated by an independent committee; ‡‡‡One malignant melanoma in situ case; ¶¶¶No drug hypersensitivity reactions were anaphylactic.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BKZ, bimekizumab; EAIR, exposure-adjusted incidence rate; IBD, inflammatory bowel disease; MACE, major adverse cardiac events; MedDRA: Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified; OLE, open-label extension; PY, patient-years; Q4W, every 4 weeks; SIB: suicidal ideation and behaviour; SS, safety set; TEAE, treatment-emergent adverse event.

B.3.11 Conclusions about comparable health benefits and safety

Bimekizumab is the only available humanised immunoglobulin antibody that binds to IL-17F in addition to IL-17A in order to inhibit the IL-17 pathway (70), a pivotal driver of inflammation in PsA (71-74).

Across the Phase 3 clinical trial programme for bimekizumab in PsA, improvements vs placebo were observed across the different disease domains of PsA at Week 16 both in populations of patients who are TNFi-IR (BE COMPLETE), or bDMARD-naïve (BE OPTIMAL). A significantly better response vs placebo was observed for the primary endpoint, ACR50, in both trials ($p<0.001$). Significant improvements were also observed for all endpoints in the statistical hierarchies at Week 16, including a higher proportion of patients achieving almost clear skin (as measured by PASI90 response), better physical function and HRQoL (change from baseline in SF-36 PCS, and HAQ-DI scores), and a higher proportion of patients achieving MDA vs placebo. BE OPTIMAL also included some additional ranked secondary endpoints; in the bDMARD-naïve trial population, bimekizumab led to the inhibition of structual progression of joint damage vs placebo (assessed by vdHmTSS), both in the high-risk and overall population. In a pooled

population of patients from BE COMPLETE and BE OPTIMAL, improvements in periarticular disease manifestations (enthesitis and dactylitis-free state by LEI and LDI, respectively) were observed after 16 weeks of treatment with bimekizumab in the subset of patients affected by enthesitis or dactylitis at baseline, respectively. A higher proportion of patients receiving bimekizumab also achieved other stringent disease activity measures at Week 16, including completely clear skin (as measued by PASI100), and composite measures across multiple disease domains including very low disease activity, and combined joint and skin (ACR50+PASI100) response. In both TNFi-IR and bDMARD-naïve patient populations, achieving more stringent levels of disease control, including ACR criteria, PASI criteria, and MDA, is associated with greater improvements in patients' physical function, and pain scores (187). A higher proportion of patients also achieved PsARC response, which is an important outcome used to determine treatment response (75, 77-79, 148-152).

Across the different disease domains, separation between bimekizumab and placebo was observed as early as Week 2 or Week 4 (the first assessment after the initial dose). Longer-term data over 52 weeks in BE COMPLETE and BE OPTIMAL shows that the response to bimekizumab treatment is sustained. The results of the supportive Phase 2 BE ACTIVE 2 study also shows the response to bimekizumab is sustained, with efficacy maintained over 3 years of treatment (174).

Importantly, consistent efficacy results were observed across both study populations, i.e. patients who are TNFi-IR, and bDMARD-naïve. These results add to the developing evidence demonstrating the efficacy of bimekizumab in rheumatology, including the BE MOBILE 1 and BE MOBILE 2 trials in non-radiographic axial spondyloarthritis, and ankylosing spondylitis, respectively (207), and the four Phase 3 trials in patients with PSO (BE VIVID, BE READY, BE SURE, and BE RADIANT) (96-98, 208).

Of note, BE OPTIMAL included an adalimumab 40 mg Q2W reference arm which was not powered for statistical comparison vs bimekizumab or placebo. This was included as adalimumab is a first-line standard comparator for new PsA treatments, and allowed active treatment-blinding to be maintained to Week 52, therefore helping reduce the associated bias for efficacy/safety assessments introduced by "unblinding". The inclusion of an adalimumab active reference arm is consistent with other pivotal PsA trials, including SPIRIT-P1 (49) investigating ixekizumab, and OPAL Broaden investigating tofacitinib (185). Although no formal statistical comparisons of bimekizumab vs adalimumab were conducted in BE OPTIMAL, bimekizumab demonstrated similar ACR20/50/70, MDA, PsARC response, and HAQ-DI change from baseline and numerically better PASI75/90/100 response at Week 52, with similar rates of discontinuations due to AEs.

Across the clinical trial programme for bimekizumab for the treatment of active PsA (BE COMPLETE, BE OPTIMAL, BE VITAL, BE ACTIVE, BE ACTIVE 2), treatment with bimekizumab 160 mg Q4W was well tolerated in adult patients with active PsA. The safety profile of bimekizumab was consistent with previous Phase 3 studies in patients with plaque PSO (172), and axSpA (207), and studies of IL-17Ai (172). No new or unexpected safety concerns or signals were observed.

As direct comparisons between bimekizumab and the proposed comparator ixekizumab cannot be made using data from BE COMPLETE, and BE OPTIMAL, evidence for the efficacy of bimekizumab is supported by the NMAs presented in Section B.3.9. In the NMAs across both patient populations, bimekizumab demonstrated statistically superior or similar treatment effects than ixekizumab across various disease domains. In patients who are TNFi-experienced, bimekizumab was statistically superior vs ixekizumab for ACR20, PASI100, PsARC response, and enthesitis resolution (according to LEI) and similar for ACR50, ACR70, PASI75, PASI90, MDA, dactylitis resolution (according to LDI), HAQ-DI, and pain VAS (Section B.3.9.4.2). In patients who are TNFi-CI, bimekizumab was statistically superior vs ixekizumab for ACR70, and PsARC, and similar for ACR20, ACR50, PASI75, PASI90, and PASI100 (Section B.3.9.4.3). In a mixed population of TNFi-experienced, and b/tsDMARD-naïve patients, bimekizumab was similar to ixekizumab for SAEs, discontinuation, and discontinuation due to AEs (Section B.3.9.4.4).

Taken together, the results of the clinical trial programme and the NMAs demonstrate the value of a well-tolerated, additional therapy with a novel mechanism of action (without the need for a loading dose) which is anticipated to provide clinicians and patients with greater treatment choices for this chronic life-long condition, reduce the clinical burden, and prevent disease progression. Importantly, the response to bimekizumab is consistent across both biologic-naïve and TNFi-CI populations.

B.3.12 Ongoing studies

BE VITAL is an ongoing, multicentre, OLE assessing the long-term safety, tolerability, and efficacy of bimekizumab in patients with active PsA; the feeder studies were BE COMPLETE and BE OPTIMAL. Bimekizumab 160 mg Q4W SC was investigated for a period of up to 140 weeks, followed by a SFU 20 weeks after the final dose of bimekizumab (209). Week 52 data from BE COMPLETE that would form part of the OLE analysis is already presented in this submission (Section B.3.6.1.1.4).

B.4 Cost-comparison analysis

The cost-comparison analysis shows that bimekizumab is expected to be cost-saving compared with ixekizumab for the treatment of adult patients with active PsA

- A cost-comparison analysis was conducted comparing bimekizumab and ixekizumab for the treatment of adult patients with active PsA who have had an inadequate response or have been intolerant to one or more cDMARDs
- Consistent with TA803 (88), the analysis only considers acquisition costs, as it is assumed that there are no differences in administration, monitoring, or AE costs, and resource use between bimekizumab and ixekizumab
- Ixekizumab was included in the analysis at the National Health Service (NHS) list price; bimekizumab was included at the confidential patient access scheme (PAS) price
- In the base case, bimekizumab results in cost savings of [redacted] vs ixekizumab in the b/tsDMARD-experienced population, and [redacted] in the TNFi-CI population
- All considered scenario analyses result in cost savings for bimekizumab vs ixekizumab in both patient populations when applying the PAS

B.4.1 Changes in service provision and management

Bimekizumab is administered as a SC injection every 4 weeks (Appendix C), with consideration given to discontinuing treatment in patients who have shown no improvement within 16 weeks of beginning treatment. Whilst NHS resource may be used to provide education in self-administration to support the first administration, all subsequent doses of bimekizumab would be administered at the patient's home, supported by a home care service provided by UCB Pharma Ltd. There is no expected cost to the NHS in England for administering bimekizumab beyond the first administration at Week 0. This is consistent with current practice for other SC-administered therapies in PsA.

It is not expected that there will be any differences in resource use between bimekizumab and the comparator treatment, ixekizumab, which is also administered every 4 weeks as a SC injection. Both treatments are available as either pre-filled pens or pre-filled syringes.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

A cost-comparison model was built in Microsoft® Excel to evaluate the cost to the NHS of using bimekizumab in comparison to ixekizumab, to treat adult patients with active PsA. Ixekizumab

was selected as the appropriate comparator for the cost-comparison, for the reasons outlined in Table 1, Section B.1.1.

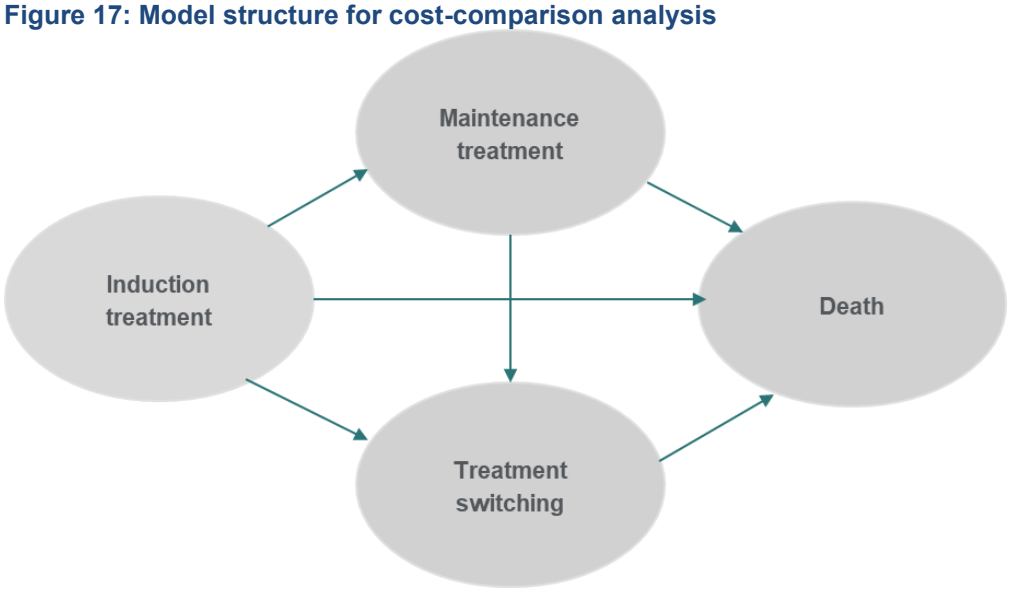
The analysis adopted a 10-year time horizon, in order to capture all relevant cost differences between the modelled treatments. This time horizon is consistent with that used for the prior cost-comparison in this indication (risankizumab [TA803]) (88). A 5-year time horizon was also explored through a scenario analysis. A 1-week cycle length is used in the model, which is appropriate for capturing the dosing schedule of each treatment as well as the timepoints for assessing treatment response. A 0% discount rate was applied to costs in the base case, in line with the cost-comparison analysis for risankizumab in TA803 (88). A 1.5% and 3.5% discount rate for costs was explored in scenario analyses (210).

This analysis included only treatment acquisition costs, as it was assumed that there were no differences in administration, monitoring, and AE costs, or resource use between bimekizumab and ixekizumab (Section B.2.2 and Section B.4.2.3). This is consistent with the cost-comparison analysis for risankizumab in TA803 (88).

B.4.2.1.1 Model structure

The structure of the cost-comparison model is outlined in Figure 17.

Figure 17: Model structure for cost-comparison analysis



The model assumes that all patients begin in the induction period of their respective treatment (bimekizumab or ixekizumab). Patients receive treatment for an initial period in line with the licensed posology and the timepoint for assessing treatment response consistent with NICE recommendations, clinical practice and/or the SmPC label (16 weeks for bimekizumab [Appendix C] and ixekizumab (77, 83)). It is assumed that patients remain on treatment within this induction

period, consistent with the assumption validated for the cost-comparison model of risankizumab in TA803 (88).

At the end of this initial period, PsARC response to each treatment is assessed. If patients are determined to have achieved a PsARC response to treatment, they are modelled to continue on treatment. PsARC has been used and accepted as a measure of response in this indication in previous NICE technology appraisals including that of ixekizumab (TA537 (89)), and the risankizumab cost-comparison (TA803 (88)). Non-responders at the end of the initial period enter the 'treatment switching' state and are assumed to discontinue treatment and incur no further costs in the model, as per TA803 (88). In reality, patients who discontinue treatment would be likely to receive alternative subsequent therapies. However, given that the PsARC response rates and discontinuation rates were assumed equal between bimekizumab and ixekizumab, costs of subsequent therapies would be equal between the modelled treatment arms and can therefore be excluded from the analysis without impacting the cost-comparison. This approach is in line with the prior cost-comparison in this indication (TA803) (88).

As noted above, the analysis assumed equal efficacy between modelled treatments. This assumption is supported by the NMA presented in Section B.3.9.4, which found bimekizumab to be comparable, or superior, to ixekizumab for all outcomes, including PsARC response rates where bimekizumab was statistically superior to ixekizumab in both the b/tsDMARD experienced and TNFi-CI populations[a]. PsARC response rates for ixekizumab at the end of the induction period were set equal in the model to that of bimekizumab from the NMA. This corresponds to a PsARC response rate of 0.85 for b/tsDMARD-experienced patients, and 0.83 for TNFi-CI patients. Scenario analyses have been presented using the PsARC response rates for ixekizumab from the NMA in both populations, and using outputs of the b/tsDMARD-naïve NMA in the TNFi-CI population.

Patients who continue into the maintenance period of treatment were modelled to have a weekly probability of discontinuing treatment of 0.35% (converted from the corresponding annual probability of discontinuation of 16.50%). This discontinuation rate was assumed to be equal between bimekizumab and ixekizumab. This assumption is consistent with the prior appraisals in this indication, in which the committee's preferred analysis assumed equivalent discontinuation rates for all treatments (Section B.2.1.3).

The death state is an absorbing state; the model allows patients to enter the death state from all other health states. General population mortality (weighted by sex based on the distribution of

[a] Please see page 19 for a reminder of the population terminology.

males/females across BE COMPLETE, and BE OPTIMAL, and adjusted using a standardised mortality ratio (SMR) [Section B.4.2.1.2]) was applied to all patients in the base-case model.

An overview of the features of the cost-comparison analysis is presented in Table 30.

Table 30: Features of the cost-comparison analysis

Component	Approach
Population	Adult patients with active PsA† 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 ▪ They have had two cDMARDs and at least one bDMARD, or ▪ TNFis are contraindicated but would otherwise be considered (as described in the NICE technology appraisal guidance on etanercept, infliximab, and adalimumab for the treatment of PsA (75)).
Intervention	Bimekizumab 160 mg administered SC Q4W
Comparator	Ixekizumab 80 mg administered SC Q4W
Outcomes	• Incremental costs per patient • Total costs per patient
Perspective	NHS and PSS in England and Wales
Time horizon	10 years • A 5-year time horizon is considered in a scenario analysis
Discounting	0% discount rate for costs • 1.5% and 3.5% annual discount rate for costs are considered in scenario analyses

†Bimekizumab is recommended as an option for treating adults with plaque psoriasis after evidence was appraised in TA723 (82). As a result of this prior analysis, the plaque psoriasis population has not been considered for analysis in this cost-comparison.
Abbreviations: bDMARD, biological disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; DMARD, disease-modifying anti-rheumatic drug; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PsA, psoriatic arthritis; PSS, personal social services; Q4W, every 4 weeks; SC, subcutaneous injection; TA, technology appraisal; TNFi, tumour necrosis factor alpha-inhibitor.

B.4.2.1.2 Baseline characteristics

Baseline characteristics taken from BE COMPLETE and BE OPTIMAL were used to estimate mortality in the model (Table 31). All-cause mortality sourced from the 2020 Office for National Statistics (ONS) life tables for England and Wales was weighted by the starting age and proportion of female patients in BE COMPLETE for TNFi-IR patients, and BE OPTIMAL for TNFi-CI patients (211). These mortality rates were then further adjusted using a SMR of 1.05 to account for an additional risk of death amongst PsA patients compared with the general population (212).

Table 31: Baseline characteristics from BE OPTIMAL and BE COMPLETE

Baseline characteristics	BE COMPLETE (172, 189)	BE OPTIMAL (55)
Age at start (years), mean	50.54	48. 65
% male	47.50	46.80
Weight (kg)	85.95	84.63

B.4.2.2 Intervention and comparators' acquisition costs

A summary of the acquisition costs for bimekizumab and ixekizumab is presented in Table 32. List prices for both treatments are sourced from the British National Formulary (BNF, 2023) (95, 213). The Patient Access Scheme (PAS) price for bimekizumab is applied in the base case, with a scenario using the list price presented.

Table 32: Acquisition costs of the intervention and comparator technologies

	Bimekizumab	Ixekizumab
Pharmaceutical formulation	160 mg solution for injection in a pre-filled syringe or pre-filled pen	80 mg solution for injection in a pre-filled syringe or pre-filled pen
(Anticipated) care setting	Secondary care/home care†	
Acquisition cost (excluding VAT)	List price: £2,443.00 for two 160 mg injections PAS price: [redacted] for two 160 mg injections	List price: £1,125.00 for one 80 mg injection
Acquisition cost per dose (excluding VAT)	List price: £1,221.50 for one 160 mg injection PAS price: [redacted] for one 160 mg injection	List price (induction phase‡): £2,250.00 for two 80 mg injections List price (maintenance phase‡): £1,125.00 for one 80 mg injection
Method of administration	SC injection	
Doses	160 mg per administration (one injection)	80 mg per administration (loading dose is 160 mg taken as two 80 mg injections)
Dosing frequency	160 mg Q4W	160 mg loading dose (induction phase), then 80 mg Q4W (maintenance phase)‡
Dose adjustments	N/A	
Average length of a course of treatment	Approximately 3 years, based on 16.50% annual discontinuation rate (Section B.4.2.1.1)	
Average cost of a course of treatment without discounting (acquisition costs only; b/tsDMARD-experienced)	List price: £65,808 PAS price: [redacted]	List price: £62,015
Average cost of a course of treatment without discounting (acquisition costs only; TNFi-CI)	List price: £64,489 PAS price: [redacted]	List price: £60,800
(Anticipated) average interval between courses of treatment	N/A	
(Anticipated) number of repeat courses of treatment	N/A	

†It is expected that NHS resource may be used to provide education in self-administration to support the first injection in a secondary care setting; all subsequent administrations would take place in the patient's home; ‡The administration of ixekizumab is subject to an induction phase in the first cycle, over a treatment duration of

4 weeks; subsequent administration is part of the maintenance phase of treatment.
Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; N/A, not applicable; NHS, National Health Service; PAS, patient access scheme; Q4W, every 4 weeks; SC, subcutaneous; TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated; VAT, value added tax.

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

Bimekizumab and ixekizumab are administered every 4 weeks by SC injection. As outlined in Section B.4.1, there is no expected cost to the NHS for administering SC injections beyond the first administration. As a result, it has been assumed in this analysis that there are no differences in NHS resource use across treatments, and hence administration costs have not been included in the model.

Furthermore, as the frequency and costs associated with monitoring of patients receiving bimekizumab is not expected to differ from ixekizumab, monitoring costs have not been included in the model. This approach is consistent with TA803 (88).

B.4.2.4 Adverse reaction unit costs and resource use

Costs and resource use associated with AEs are assumed to be similar between bimekizumab and ixekizumab and as a result, AE costs have not been included in the model. This approach is in alignment with previous TAs in this indication, including the cost comparison in TA803. It is also consistent with a post-hoc comparison of TEAEs between bimekizumab and the adalimumab reference arm, where similar rates are reported (Section B.3.10.1.1), and with the NMA on SAEs, which shows no significant differences between bimekizumab and ixekizumab.

B.4.2.5 Miscellaneous unit costs and resource use

No other costs have been included in the model.

B.4.2.6 Clinical expert validation

The assumptions on treatment efficacy, administration, monitoring, discontinuation, and safety that inform the cost-comparison model were validated by seven independent clinical, health technology assessment, and health economic experts at a UK advisory board held in August 2022 (80). Quality-control was also undertaken by an independent programmer who was not involved in the initial scoping or build of the model, in which inputs, assumptions and calculations were checked for accuracy and consistency.

B.4.2.7 Uncertainties in the inputs and assumptions

A summary of the inputs and assumptions used in the cost-comparison model is provided in Table 33 and Table 34, respectively.

Table 33: Summary of model inputs

Input	Value	Source/ reference	Explored in sensitivity/scenario analysis?
Time horizon (years)	10 years	Consistent with NICE practice, TA803 (88)	Scenario analysis (5 years)
Discount rate (%)	0%	Consistent with TA803 (88)	Scenario analyses (1.5%, 3.5%)
Starting age (years)	b/tsDMARD-experienced: 50.54 TNFi-CI 48.65	BE COMPLETE and BE OPTIMAL (175, 178)	No – age and proportion male only impact calculations of mortality in the model
Proportion male (%)	b/tsDMARD-experienced: 47.50 TNFi-CI: 46.80	BE COMPLETE and BE OPTIMAL (175, 178)	
Discontinuation rate (annual) (%)	16.50	Prior NICE TAs in PsA; (TA220 (214), TA340 (215), TA433 (216), TA445 (167), TA537 (89), TA768 (217) and TA803 (88))	No
Adverse events	Not included	Prior NICE TAs in PsA; (TA220 (214), TA340 (215), TA433 (216), TA445 (167), TA537 (89), TA768 (217) and TA803 (88))	No
Efficacy (PsARC response rate)	b/tsDMARD-experienced: 0.85 TNFi-CI: 0.83	NMA, ixekizumab set equivalent to bimekizumab (Section B.3.9.4.2 and B.3.9.4.2)	Scenario analyses (using PsARC response rates for ixekizumab from the NMA, using values from the b/tsDMARD - naïve NMA)
SMR	1.05	Ali et al, 2007 (212)	Scenario analysis (not included)
Timepoint treatment response (weeks)	16	Prior NICE TAs in PsA; TA220 (214), TA340 (215), TA433 (216), TA445 (167), TA537 (89), TA768 (217) and TA803 (88)	Scenario analysis (20 weeks for ixekizumab)
Acquisition costs (per dose)			
Bimekizumab 320 mg (two 160 mg injections)	List price: £2,443.00 PAS price: [redacted]	UCB Pharma Ltd	No – no uncertainty
Ixekizumab 80 mg (one 80 mg injection)	List price: £1,125.00	BNF	No – no uncertainty

Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; BNF, British National Formulary; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PAS, patient access scheme; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; SMR, standardised mortality ratio; TA, technology appraisal; TNFi-CI; tumour necrosis factor alpha inhibitor-contraindicated.

Table 34: Summary of key model assumptions

Assumption	Rationale	Explored in sensitivity/ scenario analysis?
The probability of achieving a PsARC response to treatment is equivalent for bimekizumab and ixekizumab	The NMA results presented in Section B.3.9.4.2 and B.3.9.4.2 demonstrate similar efficacy between modelled treatments	–
Patients remain on initial treatment until assessment of response at 16 weeks or death	This assumption is consistent with previous NICE TAs for PsA (TA433 (216), TA537 (89), TA803 (88)) and the licensed posology outlined in the SmPCs for bimekizumab (Appendix C) and ixekizumab (83)	Scenario analysis based on SmPC range for ixekizumab (20 weeks)
The annual probability of discontinuation of treatment after assessment of response at 16 weeks is 16.50% for bimekizumab and ixekizumab	This assumption is consistent with previous NICE TAs for PsA (TA220 (214), TA340 (215), TA433 (216), TA445 (167), TA537 (89), TA768 (217) and TA803 (88))	–
Administration and monitoring, and AE costs are equivalent for bimekizumab and ixekizumab and are not considered in the CCM	Bimekizumab and ixekizumab are both subcutaneously administered and no differences in monitoring are expected. A post-hoc comparison of the results reported in Section B.3.10.1.1 demonstrate that TEAEs are similar between bimekizumab and the adalimumab reference arm. Additionally, the NMA shows no significant differences in AEs between bimekizumab and ixekizumab. Therefore, drug acquisition costs are the only costs considered in the model. This approach is consistent with previous cost-comparison analyses in PsA (TA803 (88))	–

Abbreviations: AE, adverse event; CCM, cost-comparison model; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; SmPC, summary of product characteristics; TA, technology appraisal; TEAE, treatment-emergent adverse events.

B.4.3 Base-case results

The base-case results over a 10-year time horizon for the total cost of bimekizumab vs ixekizumab using the PAS price for bimekizumab, in the b/tsDMARD-experienced and TNFi-CI

populations, are presented in Table 35 and Table 36, respectively. Results using the list price for bimekizumab have been included in Appendix M.

In the b/tsDMARD-experienced population and at the PAS price for bimekizumab, the total drug acquisition costs for bimekizumab across a 10-year time horizon were [redacted]. This corresponds to a cost-saving of [redacted] vs ixekizumab.

Table 35: Base-case results: b/tsDMARD-experienced – using bimekizumab (PAS price)

Therapy	Total cost	Incremental cost of treatment with bimekizumab vs ixekizumab
Bimekizumab	[redacted]	–
Ixekizumab	£62,015	[redacted]

Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; PAS, patient access scheme.

In the TNFi-CI population and at the PAS price for bimekizumab, the total drug acquisition costs for bimekizumab across a 10-year time horizon were [redacted]. This corresponds to a cost saving of [redacted] vs ixekizumab.

Table 36: Base-case results: TNFi-CI – using bimekizumab (PAS price)

Therapy	Total cost	Incremental cost of treatment with bimekizumab vs ixekizumab
Bimekizumab	[redacted]	–
Ixekizumab	£60,800	[redacted]

Abbreviations: PAS, patient access scheme; TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated.

B.4.4 Sensitivity and scenario analyses

B.4.4.1 Scenario analysis

Results of scenario analyses explored in the model using the PAS price of bimekizumab, in the b/tsDMARD-experienced and TNFi-CI populations, are presented in Table 37 and Table 38, respectively. Decreasing the time horizon in the model from 10 years to 5 years was associated with the largest difference from the base case result. A summary of scenario analyses at the list price of bimekizumab is presented in Appendix M.

Table 37: Scenario analyses: b/tsDMARD-experienced patients – bimekizumab (PAS price) vs ixekizumab (list price)

Scenario	Difference in incremental cost	% difference
Base case	[redacted]	[redacted]
5-year time horizon	[redacted]	[redacted]
1.5% discount rate for costs	[redacted]	[redacted]
3.5% discount rate for costs	[redacted]	[redacted]
IXE PsARC response rate	[redacted]	[redacted]
No SMR adjustment	[redacted]	[redacted]

Scenario	Difference in incremental cost	% difference
IXE 20-week PsARC response assessment	[redacted]	[redacted]

Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; IXE, ixekizumab; PAS, patient access scheme; PsARC, Psoriatic Arthritis Response Criteria; SMR, standardised mortality ratio.

Table 38: Scenario analyses: TNFi-CI patients – bimekizumab (PAS price) vs ixekizumab (list price)

Scenario	Difference in incremental cost	% difference
Base-case	[redacted]	[redacted]
5-year time horizon	[redacted]	[redacted]
1.5% discount rate for costs	[redacted]	[redacted]
3.5% discount rate for costs	[redacted]	[redacted]
IXE PsARC response rate	[redacted]	[redacted]
PsARC response rate from the b/tsDMARD-naïve NMA	[redacted]	[redacted]
No SMR adjustment	[redacted]	[redacted]
IXE 20-week PsARC response assessment	[redacted]	[redacted]

Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; IXE, ixekizumab; NMA, network meta-analysis; PAS, patient access scheme; PsARC, Psoriatic Arthritis Response Criteria; SMR, standardised mortality ratio; TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated.

B.4.5 Subgroup analysis

Subgroups were not considered in the cost-comparison model.

B.4.6 Interpretation and conclusions of economic evidence

The cost-comparison analysis for bimekizumab vs ixekizumab considered drug acquisition costs to be the only differential parameter between treatments, across a 10-year time horizon. Base-case incremental costs have been presented at the PAS price for bimekizumab. Scenario analyses have demonstrated that results of the analysis are robust to structural uncertainties and variation in key assumptions made surrounding model inputs.

The results of the analysis demonstrate that bimekizumab, when provided at the PAS price, is associated with cost-savings relative to list price ixekizumab when used in adult patients with active PsA whose disease has not responded well enough to DMARDs or who cannot tolerate them, showing consistent results across either b/tsDMARD-experienced or TNFi-CI patient populations. This is under the assumption that bimekizumab and ixekizumab are equivalently effective, with the same rates of PsARC response and no differences in efficacy or adverse events that would lead to differences in resource use.

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B.6 Appendices

The following appendices are provided as separate documents to the submission:

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Price details of treatments included in the submission

Appendix I: Checklist of confidential information

Appendix J: Primary clinical effectiveness evidence

Appendix K: Endpoints commonly used in clinical trials in PsA

Appendix L: Supporting clinical effectiveness evidence

Appendix M: Base-case results and scenario analyses – bimekizumab list price

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Bimekizumab for treating active psoriatic arthritis [ID4009]

Summary of Information for Patients (SIP)

May 2023

File name	Version	Contains confidential information	Date
ID4009_Bimekizumab in PsA_SIP	1	No	30th May 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Bimekizumab (Bimzelx®)

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Adult patients with active psoriatic arthritis (PsA) whose disease has not responded well enough to disease-modifying anti-rheumatic drugs (DMARD) 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
  ○ They have had two conventional DMARDs and at least one biologic DMARD, or
  ○ Tumour necrosis factor alpha-inhibitors (TNFi) are contraindicated but would otherwise be considered (as described in the National Institute for Health and Care Excellence's [NICE] technology appraisal guidance on etanercept, infliximab, and adalimumab for the treatment of PsA (1))†
 	
†In TA199, etanercept, infliximab, and adalimumab are recommended for adults with peripheral arthritis with three or more tender joints, and three or more swollen joints whose PsA has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination. Treatment should normally be started with the least expensive drug (considering drug administration costs, required dose, and product price per dose). This may be varied for individual patients because of differences in the method of administration and treatment schedules (1).

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Bimekizumab does not yet have marketing authorisation for the indication in this submission. A regulatory submission was made to the European Medicines Agency (EMA) in August 2022. Committee for Medicinal products for Human Use (CHMP) positive opinion was received on 26/04/2023 (2). Anticipated dates for approval are provided in Document B, Table 2.

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

- Psoriasis Association: Annual corporate sponsorship – £1,500 per annum
- Consultancy for PsA patient insights generation 2022 – £3,000
- Arthritis Action: Silver Anniversary Sponsorship 2022 – £10,000
- Consultancy for PsA patient insights generation 2022 – £3,000
- Arthritis and Musculoskeletal Alliance (ARMA): Sponsorship of Best MSK local pilots 2022 – £12,000

Section 2: current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

PsA is a life-long disease that causes inflammation in the body. It affects joints, tendons, and ligaments, causing them to swell and become painful, as well as affecting the skin.

The manifestations of PsA can be broadly categorised into two categories: musculoskeletal, and non-musculoskeletal. Musculoskeletal manifestations include peripheral arthritis (affecting joints outside of the spine), inflammation of entheses (where tendons and ligaments connect to bone), and dactylitis (swelling of fingers or toes) (3). Non-musculoskeletal manifestations include skin and nail psoriasis (PSO). Most people with PsA develop PSO before the onset of PsA (~85% of patients, mean interval of 10 years), however some patients may develop arthritis before or at the same time as PSO occurs (~15% of patients) (4). PsA is also

associated with several other health problems, including uveitis (eye inflammation), and inflammatory bowel disease (5). Joint disease in PsA worsens over time (6), and can result in damage to the joints causing limited range of movement and in some cases, the joint may fuse resulting in disability. There are multiple different types of treatment available for the long-term control of PsA, with different mechanisms of action.

According to a database study of 4.8 million UK adults aged between 18–90 years, PsA commonly affects those of working age (7). In almost 7 in 10 UK patients, onset is between 30 and 60 years, with a peak prevalence between 50–59 years (7). PsA affects men and women equally (7), and up to 4 in 10 people with PSO (8-10).

PsA is associated with a significant physical and emotional burden on patients. Patients experience debilitating symptoms including pain, stiffness, and swelling in one or more peripheral joints, skin-associated symptoms (dry, itchy, and sore skin patches), and fatigue (11, 12). There is a significant association between joint damage, disability, and physical function (13), with the greatest physical impact among patients with enthesitis or dactylitis compared with all patients with PsA (14).

PsA also affects a patient's quality of life, with symptoms of joint disease, pain, fatigue, and skin disease all contributing (14-17). Patients with PsA and substantial areas of skin affected by PSO report higher disease burden and worse quality of life than those less affected by PSO (18). Other health conditions associated with PsA also have a significant impact on patient quality of life (19). Furthermore, patients with PsA are at an increased risk of developing psychological conditions (20).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Patients with suspected PsA should be referred to a rheumatologist for assessment (21). Diagnosis may be based on current symptoms, patient history, radiography (X-rays, ultrasound, or magnetic resonance imaging [MRI]), and blood tests (22). Diagnosis of PsA is difficult due to the numerous symptoms, which can overlap with other inflammatory rheumatic diseases, and symptoms may "wax and wane" over time (22). There is also no single test able to diagnose PsA.

No additional tests or investigations are required for bimekizumab.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The aim of treatments for PsA is to improve the signs and symptoms of disease (including on skin and nails), inhibit joint damage, improve quality of life, and reduce pain (23).

Treatments for PsA include physiotherapy, non-steroidal anti-inflammatory drugs (NSAID) and painkillers, steroid injections, and DMARDs which act to inhibit the causes of inflammation in the joints and skin. There are a number of different types of DMARDs that are classed as either:

- conventional DMARDs (cDMARDs; for example: methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide)
- biologic DMARDs (bDMARDs; for example: ixekizumab, secukinumab, adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, guselkumab, ustekinumab, risankizumab) or
- targeted synthetic DMARDs (tsDMARDs; for example: tofacitinib, upadacitinib, and apremilast).

These treatments need to be given by a rheumatologist who specialises in musculoskeletal conditions. Key clinical guidelines for the treatment of PsA include those published by the British Society for Rheumatology (BSR) in 2022 (24), NICE clinical guideline 65 (NG65) (21), and evidence-based recommendations from NICE (1, 25-33).

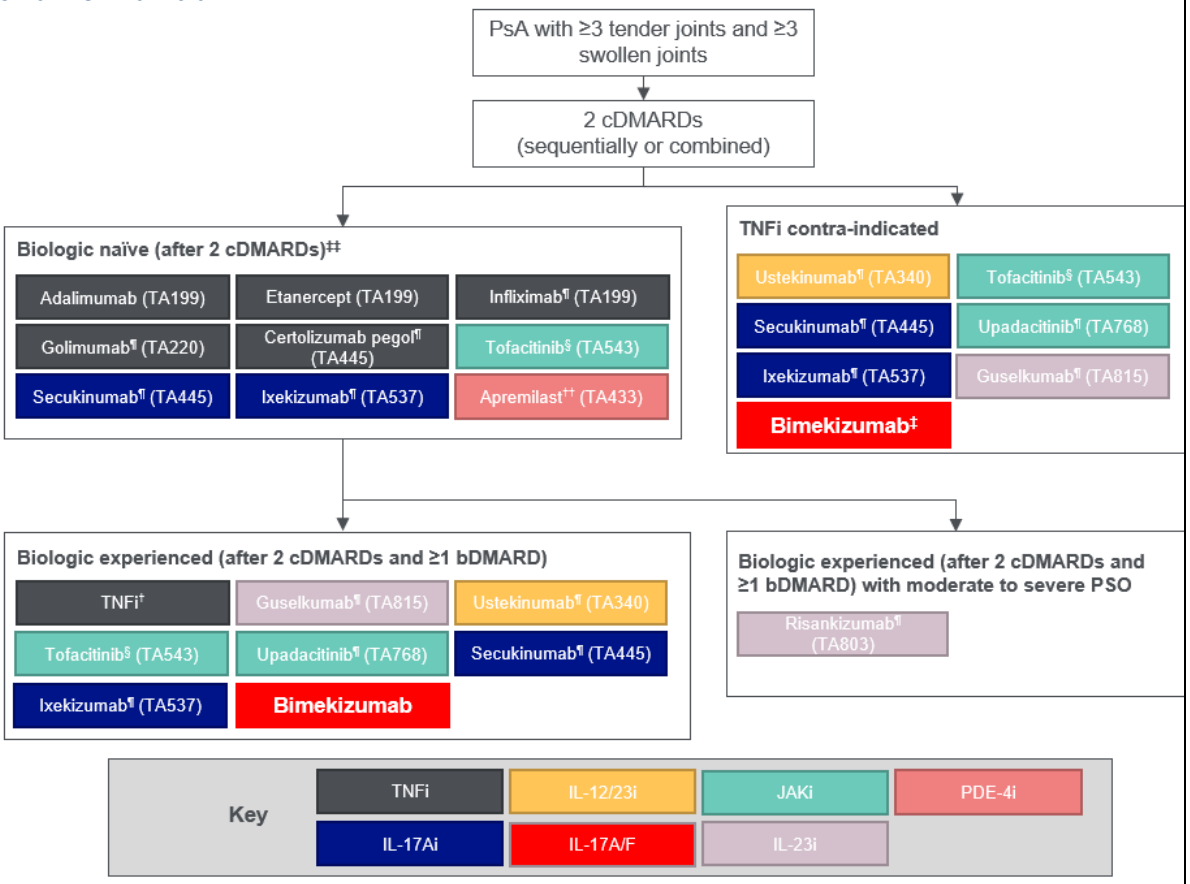
Bimekizumab is a biologic DMARD and is expected to be used in patients with PsA whose disease has not responded well enough to conventional DMARDs or who cannot tolerate them, and only if the patient has:

- Peripheral arthritis with three or more tender joints and three or more swollen joints, and
  - They have had two conventional DMARDs and at least one biological DMARD, or
  - TNFi are contraindicated but would otherwise be considered (termed TNFi-contraindicated [TNFi-CI]).

The proposed use of bimekizumab in the UK clinical pathway of care is highlighted in red in Figure 1.

Although several therapies are recommended for patients with PsA, switching between biologic/targeted synthetic DMARDs during long-term disease management is a recommended strategy for patients who do not experience a benefit to or are intolerant of one treatment (24, 34). However, there remains an unmet need for new treatments that provide an additional therapeutic option for patients with this progressive, life-long condition.

Figure 1: Current treatments for the treatment of PsA in the UK, and the proposed use of bimekizumab



Sources: NICE NG65 (21); NICE TA199 (1); NICE TA220 (25); NICE TA445 (28); NICE TA543 (29); NICE TA537 (35); NICE TA433 (27); NICE TA340 (26); NICE TA768 (32); NICE TA815 (31); NICE TA803 (33).
†Includes all TNFi recommended for biologic naïve patients; ‡The proposed positioning for bimekizumab also includes patients who are intolerant to TNFi; ¶Alone or with MTX. The positioning for guselkumab, upadacitinib, and risankizumab also includes patients who are intolerant to DMARDs; §With MTX; ††Alone or with cDMARDs; ‡‡Due to the recent availability of TNFi biosimilars as first-line therapies after non-response to adequate trials of at least two cDMARDs, non-biosimilars are not expected to be used at first-line for the majority of patients, except for those for whom TNFi are contra-indicated.
Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; i, inhibitor; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; NICE, National Institute for Health and Care Excellence; PDE-4, phosphodiesterase-4; PsA, psoriatic arthritis; PSO, psoriasis; TNF, tumour necrosis factor alpha.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

UCB has performed a quantitative study of adult patients formally diagnosed with PsA and receiving treatment to deepen the understanding of the impact of PsA on patients. The study comprised a 2-hour online focus group (five patients), and 45-minute online interviews (234 interviews) (36).

The study showed that patients suffer a range of debilitating consequences resulting from their PsA symptoms, with pain being the most common (98% of study respondents), followed by stiffness (especially first thing in the morning; 65%), fatigue (62%), reduced mobility (55%), and feeling low (55%). Patients reported that joint-related symptoms have a greater physical impact, while skin-related symptoms have a greater emotional impact. Though patients experience the interconnectivity of joint and skin symptoms differently, the majority feel there is some interrelation, with 40% identifying with 'joint and skin symptoms are intertwined, impacting one another'. Activities such as dressing, cooking and eating, work, and hobbies can all be negatively impacted by PsA symptoms. The negative impacts of PsA span from simple household chores, to moving around independently and caring for dependents. Many patients also reported that they have developed other health conditions (for example, weight gain) as a result of their PsA (64%), feel that they are no longer themselves (59%), have not been able to care for or play with children or grandchildren as much as they would like (58%), and feel stigmatised (45%). Patients also report that their PsA can have a negative impact on developing and maintaining relationships with loved ones, on their social lives, and on their career aspirations.

Almost two-thirds of patients have reported that they would prefer a treatment that slowly alleviates all symptoms versus quick relief of just some. When asked about their three most important symptoms to be relieved when setting treatment goals, 63% of patients set goals related to symptom relief, with the most common being pain in central joints (72%), localised pain in peripheral joints (67%), lower back pain (62%), psoriasis/dry itchy skin (51%), and tenderness, pain and swelling over tendons (51%).

Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Cytokines are proteins of the immune system that play an important role in co-ordinating and regulating immune responses in the body. In PsA, certain cytokines can become overactive resulting in inflammation in the joints, tendons, ligaments, and skin. Biologic treatments act to target the cytokines that are increased in PsA, thereby reducing inflammation and the symptoms of PsA.

Two key cytokines, interleukin (IL)-17A & IL-17F, are increased in patients with PsA, and play an important role in driving inflammation and harmful bone formation (37-39). Other cytokines such as tumour necrosis factor alpha (TNF-α), IL-12/23, IL-23 have been shown to also play a role in PsA. Other treatments are available that target these cytokines.

Bimekizumab, a biologic treatment, specifically targets IL-17A & IL-17F, and is the first biologic designed to selectively block both IL-17A and IL-17F (40). This prevents the activation of the subsequent inflammatory cascade, thereby reducing inflammation associated with PsA and the associated symptoms.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☒Yes

☐No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Bimekizumab can be used alone or in combination with methotrexate. Methotrexate is an immunosuppressant (conventional DMARD); it slows down the body's immune system to help reduce inflammation.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dose of bimekizumab (IL-17A & F inhibitor) for adult patients with active PsA is 160 mg every 4 weeks (41). This is administered as one injection under the skin.

Ixekizumab (IL-17A inhibitor) is also administered as an injection under the skin. The first dose is administered as two 80 mg injections, followed by one 80 mg injection every 4 weeks thereafter (42).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The clinical evidence for bimekizumab for the treatment of PsA comes from two Phase 3 randomised controlled trials (RCT):

- BE COMPLETE (NCT03896581) in patients who have had a previous inadequate response or intolerance to TNFi therapy for PsA or PSO (termed TNFi-inadequate responders [IR]; N=400) (43), and
- BE OPTIMAL (NCT03895203) in patients who have not received a current or prior biologic for the treatment of PsA or PSO (termed biologic DMARD-naïve; N=852) (44).

A summary of the trial methodologies is provided in Table 1.

Table 1: BE COMPLETE and BE OPTIMAL: overview of study design

	BE COMPLETE (43)	BE OPTIMAL (44)
Study design†	A 16-week Phase 3, multicentre, randomised, double-blind, placebo-controlled trial	A 52-week Phase 3, multicentre, randomised, double-blind, placebo-controlled, active reference‡ study comprising a 16-week double-blind placebo-controlled period, and a 36-week treatment blind period
Intervention	Bimekizumab 160 mg once every 4 weeks	
Comparators	Placebo	
Reference arm	None	Adalimumab 40 mg once every 2 weeks (trial not statistically powered for comparison)
Settings and locations where data were collected	92 sites across: Australia, Canada, Czech Republic, Germany, Hungary, Italy, Japan, Poland, Russia, United Kingdom, United States	135 sites across: Australia, Belgium, Canada, Czech Republic, France, Germany, Hungary, Italy, Japan, Poland, Russia, Spain, United Kingdom, United States

Key inclusion criteria	• Adults ≥18 years of age
	• Documented diagnosis of adult-onset, active PsA:
	  ○ Meeting the CASPAR classification criteria¶ for PsA for 6 or more months prior to screening for entry to the study
	  ○ A tender joint count of three or more out of 68 possible joints, and a swollen joint count of three or more out of 66 possible joints (dactylitis of a digit counts as 1 joint each)
	• Negative for rheumatoid factor and anti-CCP antibodies (proteins that are found in patients with rheumatoid arthritis but are usually absent in patients with PsA)
	• 1 or more active psoriatic lesion(s) and/or documented history of PSO	

	• History of inadequate response (lack of efficacy after 3 or more months of therapy at an approved dose) or intolerance to treatment with 1 or 2 TNFi for either PsA or PSO	• Patient considered by investigator to be a suitable candidate for treatment with adalimumab per regional labelling and had no contraindications to receive adalimumab as per the local label
Key exclusion criteria	• Current or prior exposure to any biologics except TNFi for the treatment of PsA or PSO, including participation in a bimekizumab clinical study (who received 1 or more dose of a product under investigation, including placebo)	• Current or prior exposure to any biologics for the treatment of PsA or PSO, including participation in a bimekizumab clinical study (who received 1 or more dose of a product under investigation, including placebo)

†During the double-blind period in both studies, neither the patient or the researcher knew which treatment the patient was receiving. During the treatment-blind period in BE OPTIMAL, the treatment was administered by unblinded researchers; ‡An active reference study includes a treatment arm where the treatment is considered to be effective by healthcare professionals (the adalimumab arm in BE OPTIMAL), however the researchers did not plan to perform any formal statistical comparisons versus bimekizumab or placebo; ¶A set of diagnostic rules proposed by experts, based on an international study of patients with PsA and other types of inflammatory arthritis.
Abbreviations: anti-CCP, anti- cyclic citrullinated peptide; CASPAR, The Classification Criteria for Psoriatic Arthritis; PsA, psoriatic arthritis; PSO, psoriasis; TNFi, tumour necrosis factor alpha inhibitor.

The long-term efficacy and safety of bimekizumab is continuing to be evaluated in the open-label extension study, BE VITAL (NCT04009499), enrolling patients who completed BE COMPLETE, and BE OPTIMAL.

Supportive evidence for the NICE submission, providing efficacy and safety data for bimekizumab over a period of 3 years, is provided by the Phase 2 study BE ACTIVE (NCT03347110; N=206) (45), and the open-label extension BE ACTIVE 2 (NCT03347110) (46).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

BE COMPLETE (in TNFi-IR patients) and BE OPTIMAL (in biologic DMARD-naïve patients) demonstrated that bimekizumab is superior to placebo in improving the signs and symptoms of PsA (Document B, Section B.3.6).

In both clinical trials, the primary endpoint was the proportion of patients achieving the American College of Rheumatology 50 (ACR50) response criteria at Week 16. ACR50 is a measure used to assess the effectiveness of treatments for PsA. It measures PsA symptoms such as joint swelling, joint tenderness, pain, and stiffness. ACR50 means that a patient has experienced a 50% improvement in the number of tender or swollen joints, and 50% improvement in at least three of the following: a patient's opinion of their overall health, a doctor's opinion of the patient's overall health, patient pain scale, a questionnaire measuring disability/physical function (health assessment questionnaire-disability index [HAQ-DI]), and acute phase reactant (change in protein indicators of inflammation). Achieving increasingly higher response thresholds, such as ACR50, has been shown to result in greater improvements in physical function, pain, and quality of life than achievement of measures corresponding to lower response thresholds (47, 48).

Both trials met their primary endpoint, with significantly more patients receiving bimekizumab achieving ACR50 response than placebo (Document B, Section B.3.6.1.1.1, and B.3.6.1.2.1). An odds ratio (OR) is a relative measure of the effect between receiving bimekizumab or placebo and achieving ACR50, with an OR greater than one meaning the odds of achieving ACR50 are greater with bimekizumab than placebo.

- In BE COMPLETE: 43% of patients receiving bimekizumab vs 7% receiving placebo achieved ACR50 at Week 16, with an OR of 11.1 ($p<0.001$)
- In BE OPTIMAL: 44% of patients receiving bimekizumab vs 10% receiving placebo achieved ACR50 at Week 16, with an OR of 7.1 ($p<0.001$)

Across both trials, bimekizumab also demonstrated statistically significant and clinically meaningful improvements vs placebo across other joint outcomes, skin outcomes, quality of life/physical function outcomes, composite measures which assess multiple signs and symptoms of disease, inhibition of structural progression (worsening) of joint damage, and enthesitis or dactylitis resolution (Document B, Section B.3.6).

The improvements with bimekizumab were seen as early as the first assessment after one dose of bimekizumab (Week 2 or Week 4) and were sustained long-term, as shown by 52-week data. Results from the completed Phase 2 studies, BE ACTIVE (45) and BE ACTIVE 2 (46) also show the response to bimekizumab is sustained, with efficacy maintained over 3 years of treatment (46).

Importantly, data from clinical studies of current advanced therapies show that a high proportion of TNFi-experienced, and biologic DMARD-naïve patients fail to achieve measures of joint, and skin disease corresponding to higher response thresholds after 24-weeks of treatment. This includes ACR50, Psoriasis Area and Severity Index (PASI) 90, and PASI100 (49-51). PASI score is a tool which measures the severity and extent of PSO; achievement of PASI90 corresponds to almost clear skin, while PASI100 corresponds to clear skin. This suggests that, currently, joint and skin manifestations are not treated optimally. In addition, switching between biologic/targeted synthetic DMARDs during long-term disease management is a recommended strategy for patients who do not experience a benefit to or are intolerant of one treatment (24, 34). Several studies have reported that patients who switch to a second TNFi have significantly poorer response and/or measures of disease activity compared with non-switching patients (52-54). Furthermore, a systematic literature review (SLR) has reported that although IL-17A inhibitors and IL12/23 inhibitors are still efficacious for patients who had failed or were intolerant to TNFi, their efficacy is lower than when used by patients who had not previously received a TNFi (55). BE COMPLETE shows that bimekizumab remains effective in patients who have had an inadequate response to prior TNFi (43).

A limitation of the Phase 3 bimekizumab clinical trials is that they were designed to make reliable statistical comparisons of bimekizumab with placebo, and not another treatment (the adalimumab reference arm was not included in BE OPTIMAL to make any formal statistical comparisons). However, this is typical of the disease area and RCTs for other therapies. Because of the absence of head-to-head data versus ixekizumab, a network meta-analysis (NMA) was conducted to provide a comparison of bimekizumab vs ixekizumab. NMA is a statistical technique used to compare multiple treatments simultaneously by combining evidence from different clinical trials using systematic methods.

In the NMA, bimekizumab provided statistically superior or similar treatment effects vs ixekizumab across different signs or symptoms of PsA in TNFi-experienced and TNFi-CI populations. Bimekizumab also demonstrated a similar risk of serious adverse events, treatment discontinuation, and discontinuation due to adverse events vs ixekizumab in a mixed patient population (TNFi-experienced, and biologic/targeted synthetic DMARD-naïve).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the clinical trial programme, various measures were used to assess the effect of treatment with bimekizumab on patient physical function/quality of life. These included:

- Short-form 36 (SF-36) physical component summary (PCS): a patient reported survey of health-related quality of life that is divided across eight domains: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, social functioning, general mental health, role limitations due to emotional problems, and vitality. Two component scores are derived from these eight domains: physical health component, and mental health component
- HAQ-DI: a measure of functional capacity, measuring the degree of difficulty dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities.

In BE COMPLETE and BE OPTIMAL, patients experienced an improvement in physical function compared with placebo at Week 16 (as measured by the SF-36 PCS and HAQ-DI) (43, 44), which were sustained over time to Week 52 (Document B, Section B.3.6). Patients also reported greater improvements in pain and fatigue vs placebo (43, 44). In the long-term study BE ACTIVE 2, physical function and quality of life with bimekizumab improved up to 3 years (56).

Results of the TNFi-experienced NMA showed that the impact of bimekizumab on a patient's quality of life is similar to ixekizumab (Document B, Section B.3.9.4).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could

potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Treatment with bimekizumab is generally well tolerated in patients with active PsA, with no new or unexpected safety concerns or signals observed across the clinical development programme. In total, 4,821 patients have been treated with bimekizumab in blinded, and open-label clinical studies for PsA, plaque PSO, and axial spondyloarthritis, representing 8,733 patient years of exposure (the number of years each patient was exposed bimekizumab added together) (41). Over 3,900 patients were exposed to bimekizumab for at least 1 year, and the safety profile was consistent across all of the diseases.

The rates of treatment discontinuation due to treatment emergent adverse events were low in BE COMPLETE and BE OPTIMAL during the double-blind treatment period to Week 16, and in BE OPTIMAL, during the overall treatment period to Week 52 (Document B, Section B.3.10).

After 16 weeks in BE COMPLETE, the most frequently reported treatment-emergent adverse events with bimekizumab included nasopharyngitis, oral candidiasis, and upper respiratory tract infection (Document B, Section B.3.10.1.1.1). After 52 weeks in BE OPTIMAL, the most frequently reported treatment-emergent adverse events with bimekizumab were nasopharyngitis, upper respiratory tract infection, urinary tract infection, headache, oral candidiasis, and diarrhoea (Document B, Section B.3.10.1.2.1).

Long-term data over a period of 3-years from BE ACTIVE and BE ACTIVE 2 also showed the safety profile of bimekizumab was consistent with previous reports, with no new safety signals identified (Document B, Section B.3.10.2.1).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The aim of treatment for PsA is to improve the signs and symptoms of disease (including on skin and nails), inhibit joint damage, improve quality of life, and reduce pain (23). Patients with PsA experience different signs and symptoms, with current treatments achieving different levels of effectiveness on each (24). Currently, a high proportion of both TNFi-experienced (49), and biologic DMARD-naïve (50, 51) patients do not reach outcomes that correspond to higher response thresholds in joints and skin. Bimekizumab has demonstrated consistent and sustained efficacy on the joint and skin measures that correspond to higher response thresholds in patients with PsA (Document B, Section B.3.6).

Clinical guidelines recommend selecting treatment based on the most severe or impactful PsA symptoms with the goal of remission or low disease activity (57). Importantly, many patients (both TNFi-IR, and biologic DMARD-naïve) do not achieve remission or low disease activity across their multiple symptoms (58). Uncontrolled disease can result in irreversible joint damage, and functional impairment (59). In the Phase 3 PsA clinical trials, ~45% of patients

achieved minimal disease activity (MDA; a composite outcome across multiple symptoms) with bimekizumab by Week 16, regardless of prior biologic use. Therefore, bimekizumab may provide another treatment option to help address the unmet need for therapies which help patients achieve MDA.

PsA is a chronic life-long condition, with an early age of onset. In the real-world, a high proportion of patients require switching to another therapy. In a UK-based study, only 56% of patients remained on their first TNFi after a mean of 4.5 years (60). Switching between biologic/targeted synthetic DMARDs during long-term disease management is a recommended strategy for patients who do not experience a benefit to or are intolerant of one treatment (24, 34). However, efficacy of current therapies may be attenuated in patients who have received previous TNFi (52-55). Importantly, consistent efficacy results were observed across both study populations in BE COMPLETE and BE OPTIMAL, in patients who are TNFi-IR, and biologic DMARD-naïve (Document B, Section B.3.6).

In the PsA clinical trials, the response to bimekizumab is rapid (with a clinically meaningful difference vs placebo often occurring as early as the first visit after the first dose of bimekizumab), and the response with bimekizumab is sustained long-term. This is particularly important, as PsA is a chronic, life-long disease with an early age of onset.

In the absence of any head-to-head data versus ixekizumab, NMA has shown that bimekizumab provided statistically significant or similar treatment effects vs ixekizumab across different disease symptoms in both TNFi-experienced and TNFi-CI patient populations. Bimekizumab also demonstrated a similar risk of serious adverse events, treatment discontinuation, and discontinuation due to adverse events vs ixekizumab in a mixed patient population (TNFi-experienced, and biologic/targeted synthetic DMARD-naive) (Document B, Section B.3.9.4). Taken together, the results of the clinical trial programme and the NMAs demonstrate that bimekizumab is a well-tolerated therapy, anticipated to provide clinicians and patients with greater treatment choices for this chronic life-long condition, reduce the clinical burden, and prevent disease progression.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Bimekizumab is delivered via a subcutaneous injection (under the skin), which may lead to pain near the injection site for a couple of days afterwards. Most other treatments for PsA are also delivered by injection, and hence, bimekizumab's method of administration is unlikely to increase the burden on patients compared with currently available treatments.

As with all treatments there can be side-effects. Side-effects that patients may experience when taking bimekizumab are listed above in Section 3g, and discussed in more detail in Document B, Section B.3.10.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

The chosen model follows a 'cost-comparison' approach. The model only considers the acquisition costs associated with bimekizumab and ixekizumab. Efficacy, as well as the costs associated with monitoring, adverse events, and administration of the treatments are assumed to be equivalent, consistent with the approach taken in the previous cost-comparison model in PsA (61).

The model only considers costs for patients that are on treatment. All patients are assumed to remain on treatment for an initial 16 weeks, at which point the Psoriatic Arthritis Response Criteria (PsARC) response to treatment is assessed. PsARC is a tool used to monitor and evaluate PsA, consisting of a physical exam and assessments made by a patient and their doctor, divided into four categories analysing: joint tenderness, joint swelling, the patient's opinion of their overall health, and the doctor's opinion of the patient's overall health. Patients who do not achieve a PsARC response ('non-responders') are assumed to discontinue treatment at 16 weeks, whilst for responders' to treatment, a weekly rate of discontinuation is assumed. PsARC response rates differ for patients that are 'TNFi-CI' (for whom TNFi are contraindicated but would otherwise be considered) and 'biologic/targeted synthetic DMARD-experienced' (that have previously received at least one biologic DMARD). Results of the cost-comparison model have been assessed separately for patients in these two groups.

A weekly probability of mortality, similar to that experienced in the general population is assumed for all patients in the model.

Modelling how much a treatment extends life and improves quality of life

Bimekizumab and ixekizumab are assumed to have equivalent efficacy; the model therefore does not consider extension to life or improvement in quality of life.

Modelling how the costs of treatment differ with the new treatment

Bimekizumab and ixekizumab are associated with different acquisition costs; however, the true difference is not known as both treatments are available to the National Health Service (NHS) with confidential discounts (known as a patient access scheme).

Bimekizumab and ixekizumab are both administered as subcutaneous injections every 4 weeks – costs associated with drug administration and monitoring are therefore expected to be the same.

Adverse events (and related costs) are also assumed to be equivalent between the two treatments.

Uncertainty

Key assumptions are that bimekizumab and ixekizumab have equivalent efficacy, and equivalent administration, monitoring, and adverse event costs. It is also assumed that the probability of discontinuation after assessment of response to treatment is the same for bimekizumab and ixekizumab.

Cost-comparison results

At list prices (that is, not including confidential patient access scheme discount for either treatment), bimekizumab is associated with similar, but slightly increased, costs to ixekizumab in both the TNFi-CI and biologic/targeted synthetic DMARD-experienced populations.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a ‘step change’ in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

The treatments currently recommended by NICE for patients with PsA include IL-17A inhibitors, such as ixekizumab. Bimekizumab targets both IL-17A, and IL-17F, which are both independent, key drivers of inflammation in PsA (38). Therefore, based on in vitro data (outside of a living organism), the inhibition of both IL-17A and IL-17F with bimekizumab may lead to a greater reduction in inflammation than inhibiting IL-17A alone (37, 38).

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

No equality issues are expected with bimekizumab.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

1. The Psoriasis and Psoriatic Arthritis Alliance (PAPAA) Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
2. The Psoriasis Association www.psoriasis-association.org.uk
3. Versus Arthritis www.versusarthritis.org
4. Efficacy and safety results (up to Week 16) for BE COMPLETE: Bimekizumab in patients with active psoriatic arthritis and previous inadequate response or intolerance to tumour necrosis factor-α inhibitors: a randomised, double-blind, placebo-controlled, phase 3 trial (BE COMPLETE) - The Lancet
5. Efficacy and safety results (up to Week 24) for BE OPTIMAL: Bimekizumab in patients with psoriatic arthritis, naive to biologic treatment: a randomised, double-blind, placebo-controlled, phase 3 trial (BE OPTIMAL) - The Lancet
6. Efficacy and safety results for BE ACTIVE: Bimekizumab in patients with active psoriatic arthritis: results from a 48-week, randomised, double-blind, placebo-controlled, dose-ranging phase 2b trial - The Lancet

7. Efficacy and safety results for BE ACTIVE 2: Safety and Efficacy of Bimekizumab in Patients With Active Psoriatic Arthritis: Three-Year Results From a Phase IIb Randomized Controlled Trial and Its Open-Label Extension Study - PubMed (nih.gov)

Further information on NICE and the role of patients:

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

American College of Rheumatology 50 (ACR50): Measures a 50% improvement in the number of tender or swollen joints, and 50% improvement in at least three of the following: a patient's opinion of their overall health, a doctor's opinion of the patient's overall health, patient pain scale, a questionnaire measuring disability/physical function (health assessment questionnaire-disability index), and acute phase reactant (change in protein indicators of inflammation)

Active reference: An active reference study includes a treatment arm where the active reference treatment is considered to be effective by healthcare professionals, however the researchers did not plan to perform any formal statistical comparisons versus the other drugs in the trial

Adverse event: An unintended or unfavourable sign, symptom, or disease in a patient who has been administered therapy (may or may not be drug-related)

Biologic: Drugs made from a living organism or its products

Blinding: the concealment of group allocation from one or more individuals involved in a clinical research study. Double-blinding means that doctors and their patients do not know which treatment patients are receiving.

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease

Chronic disease: A long-term condition that requires ongoing management over a period of years or decades, that cannot currently be cured but can be controlled with medication and/or other therapies

Dactylitis: The swelling of an entire digit (fingers, toes)

Efficacy: The measurement of a medicine's desired effect under ideal conditions, such as in a clinical trial

Enthesitis: Inflammation of sites where tendons or ligaments insert into bones

European Medicines Agency: An organisation that evaluates and monitors medicines within the European Union and the European Economic Area

Inflammation: A normal part of the body's defence to injury or infection, and, in this way, it is beneficial. But inflammation is damaging when it occurs in healthy tissues or lasts too long

Network meta-analysis: A technique used to compare multiple treatments simultaneously by combining evidence from different clinical trials

NICE: The National Institute for Health and Care Excellence is an independent organisation set up by the Government to decide which drugs and treatments are available on the NHS in England

Musculoskeletal: Relating to the musculature and skeleton

Non-musculoskeletal: Not relating to the musculature or skeleton

Psoriasis Area and Severity Index (PASI): A tool used to measure the severity and extent of psoriasis. PASI90 refers to an improvement of 90% or more in a patient's score (indicating almost clear skin), and PASI100 refers to an improvement of 100% (indicating clear skin)

Peripheral arthritis: Arthritis affecting the peripheral joints (not in the area of the spine, for example the shoulder, knee, and ankle)

Psoriatic arthritis response criteria (PsARC): A tool used to monitor and evaluate PsA, consisting of a physical exam and assessments made by a patient and their doctor divided into four categories analysing: joint tenderness, joint swelling, the patient's opinion of their overall health, and the doctor's opinion of the patient's overall health

Psoriasis: An inflammatory skin condition that causes itchy, flaky patches of skin

Quality of life: A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living

Physical function: the ability to perform basic, and instrumental activities of daily living

Progressive disease: a disease that worsens, grows or spreads over time

Randomised controlled trial: A trial where patients are randomly assigned to groups to test a specific drug, treatment or intervention

Systematic literature review: A technique to systematically select, and appraise research to answer a specific question

Treatment-emergent adverse event: an adverse event that began after the start of the trial medication

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. National Institute for Health and Care Excellence. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis – TA199 guidance. Available at: https://www.nice.org.uk/guidance/ta199 (last accessed July 2022). 2010.
2. European Medicines Agency. Bimzelx. Available at: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/bimzelx-1#:~:text=Opinion-,Opinion,product%20is%20UCB%20Pharma%20S.A. (last accessed May 2023). 2023.
3. Kishimoto M, Deshpande GA, Fukuoka K, Kawakami T, Ikegaya N, Kawashima S, et al. Clinical features of psoriatic arthritis. Best Pract Res Clin Rheumatol. 2021;35(2):101670.
4. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic Arthritis. N Engl J Med. 2017;376(10):957-70.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Bimekizumab for treating active psoriatic arthritis [ID4009]

Clarification questions

June 2023

File name	Version	Contains confidential information	Date
ID4009 bimekizumab clarification questions to PM for company [CONFIDENTIAL]_RESPONSE	**1**	**Yes**	**15th June 2023**

Section A: Clarification on effectiveness data

Network meta-analysis

A1. Priority question: Please provide the full JAGS code used for the network meta-analysis (NMA) models

The full Just Another Gibbs Sampler (JAGS) code for the network meta-analysis (NMA) models used (binominal and continuous) is provided in Appendix A. A seed of 1 was systematically used to ensure reproducibility of the results.

A2. Priority question: Company submission (CS) Appendix D.1.11 states that potential treatment-effect modifiers were identified through a gap analysis of baseline characteristics. Please provide further details on the methodology of this analysis, summarise the evidence for treatment effect modifiers and indicate whether clinicians were invited to comment on the plausibility of the potential treatment-effect modifiers or to provide suggestions of other possible treatment-effect modifiers.

A comprehensive gap analysis was performed by systematically reviewing all publicly available submissions in psoriatic arthritis (PsA), focussing on sources such as the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Pharmaceutical Benefits Advisory Committee (PBAC). Additionally, a thorough examination of all published NMAs in PsA was conducted through a systematic literature review (SLR).

The gap analysis involved extracting crucial information from all identified health technology assessment (HTA) and NMA articles, encompassing various aspects such as comparators, outcomes, likely treatment effect modifiers (where reported) and approaches. A meticulous comparison of included networks was carried out, focussing on specific outcomes. Additionally, the varying methodologies employed across the studies were summarised. It is important to note that no physician input was sought during the gap analysis process, but this was done later as part of the feasibility assessment for the NMA.

Based on the gap analysis, the following potential treatment-effect modifiers were identified: duration of disease, years of active disease, disease severity, use of prior disease-modifying anti-rheumatic drugs (DMARD), use of concomitant medications, disease status, geography, gender, psychological support, and study year (due to changes in baseline characteristics of PsA population across the year).

All treatment-effect modifiers were thoroughly investigated and documented during the NMA (1). Whenever feasible, a summary of these modifiers was included as part of the quantitative heterogeneity assessment, specifically, when the variable was reported in at least one-third of the included studies.

The suggested studies and outcomes for inclusion in the NMA, as well as the trial populations and potential treatment effect modifiers, were discussed with clinicians at the feasibility stage and their feedback was used to develop the finalised networks.

Furthermore, incorporating feedback obtained from HTA submissions and clinicians, the study identified certain key populations that warranted separate analysis to mitigate bias. These populations included the biologic/targeted synthetic DMARD (b/tsDMARD)-naïve population, tumour necrosis factor alpha-inhibitor (TNFi)-experienced population, and TNFi-contraindicated (TNFi-CI) population. As a result, the company conducted separate NMAs for each population as distinct scenarios. Further exploration of heterogeneity is provided in the response to question A6. To avoid bias around the timepoints of included data, separate NMAs were conducted for efficacy outcomes using Week 12–24 data in the base case, and Week 12–16 data in scenario analyses which can be found in the separate NMA reports submitted in the reference pack (1, 2).

A3. CS Appendix D.1.11 states that meta-regression will address various causes of uncertainty including “time since diagnosis”, and “concomitant use of MTX”. Please clarify this because our understanding is that meta-regression is only conducted on placebo response / baseline risk.

Although there was heterogeneity observed among the baseline characteristics, none of the highly heterogeneous baseline characteristics were identified as confounders of treatment effect. 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.

According to Section 4.4 of the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 3 guidelines (3), a common oversight is the failure to incorporate the correlation between treatment effect and baseline risk for the population. The guidelines propose a model parametrisation to address the heterogeneity in baseline risk across the patient population. In line with this approach, UCB employed a similar methodology to account for the baseline characteristics, instead of separately modelling each individual baseline characteristic and its impact on treatment effect. This approach aligns with the methodology employed in TA711 for guselkumab in patients with active PsA who have received at least two conventional DMARDs (cDMARD) in which the preferred meta-regression explored was adjustment for baseline risk (placebo response) (4).

A4. CS B.3.9.3.1 states that the analyses were controlled for placebo response using meta-regression. Please provide a graph or table summarising how baseline risk varied across studies.

The response rate or mean change from baseline for the placebo arm in each trial included in the NMA is presented in Table 1 to Table 4. This provides a comprehensive overview of the baseline risk across studies for each outcome and facilitates a thorough examination of the variations in baseline risk across different networks.

Table 1: TNFi-experienced, baseline risk – placebo response rate

Study	ACR20	ACR50	ACR70	PASI75	PASI90	PASI100	PsARC	MDA	VLDA
RAPID-PsA	12%	4%	4%	5%	5%	5%	12%	4%	–
PSUMMIT 2	13%	6%	2%	2%	–	–	26%	–	–
PALACE 1	5%	–	–	–	–	–	–	–	–
PALACE 2	9%	–	–	–	–	–	–	–	–
PALACE 3	13%	–	–	–	–	–	–	–	–
OPAL Beyond	24%	15%	10%	14%	–	–	29%	15%	–
SPIRIT-P2	20%	6%	3%	10%	6%	6%	20%	6%	1%
FUTURE 3	20%	7%	–	–	–	–	–	–	–
FUTURE 4	11%	7%	–	–	–	–	–	–	–
FUTURE 5	18%	7%	6%	–	–	–	–	–	–
ASTRAEA	27%	11%	5%	10%	–	–	–	–	–
Select-PSA-2	21%	6%	1%	16%	8%	6%	36%	5%	1%
BE COMPLETE	16%	7%	1%	10%	7%	5%	31%	6%	2%
COSMOS	17%	5%	1%	9%	8%	4%	–	3%	1%
KEEPsAKE 2	23%	5%	3%	–	9%	–	–	6%	–
BE ACTIVE	11%	11%	11%	14%	14%	14%	33%	11%	10%
DISCOVER 1	18%	5%	3%	8%	8%	0%	–	3%	–
FUTURE 2	14%	9%	3%	8%	8%	–	–	3%	3%

Abbreviations: ACR, American College of Rheumatology; MDA, minimal disease activity; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; TNFi, tumour necrosis factor alpha-inhibitor; VLDA, very low disease activity.

Table 2: TNFi-experienced, baseline risk – placebo response rate or mean change from baseline for placebo

Study	Enthesitis rate	Dactylitis rate	FACIT-F mean change from baseline	Pain VAS mean change from baseline
RAPID-PsA	26%	–	–	–10.2
PSUMMIT 2	–	–	–	–
PALACE 1	–	–	–	–
PALACE 2	–	–	–	–
PALACE 3	–	–	–	–
OPAL Beyond	22%	–	3	–7.72
SPIRIT-P2	29%	36%	–	–11.9
FUTURE 3	–	–	–	–
FUTURE 4	–	–	–	–
FUTURE 5	–	–	–0.1	–3
ASTRAEA	–	–	2.96	–
Select-PSA-2	22%	39%	1.3	–5
BE COMPLETE	22%	43%	0.12	–4.5
COSMOS	19%	33%	–	–
KEEPsAKE 2	26%	38%	1	–3.1
BE ACTIVE	–	13%	–	–
DISCOVER 1	–	–	–	–
FUTURE 2	–	–	–	–

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; TNFi, tumour necrosis factor alpha-inhibitor; VAS, visual analogue scale.

Table 3: TNFi-CI, baseline risk – placebo response rate

Study	ACR20	ACR50	ACR70	PASI75	PASI90	PASI100	PsARC
PSUMMIT 1	20%	9%	2%	–	–	–	36%
PSUMMIT 2	12%	7%	5%	–	–	–	38%
PALACE 1	24%	–	–	–	–	–	–
PALACE 2	21%	–	–	–	–	–	–
PALACE 3	21%	–	–	–	–	–	–
SPIRIT-P1	26%	12%	3%	7%	1%	1%	32%
OPAL Broaden	33%	10%	5%	15%	–	–	45%
FUTURE 3	19%	6%	–	–	–	–	–
FUTURE 4	21%	6%	–	–	–	–	–
FUTURE 5	31%	9%	3%	–	–	–	–
ASTRAEA	27%	15%	9%	–	–	–	–
DISCOVER 2	34%	9%	1%	–	10%	3%	45%

Study	ACR20	ACR50	ACR70	PASI75	PASI90	PASI100	PsARC
Select-PSA-1	42%	16%	4%	21%	12%	7%	55%
ACTIVE	20%	5%	1%	–	–	–	–
BE OPTIMAL	25%	10%	4%	13%	3%	2%	40%
CHOICE	23%	6%	2%	16%	9%	2%	–
KEEPsAKE 1	33%	11%	3%	–	9%	–	–
MAXIMISE	19%	–	8%	–	–	–	–
KEEPsAKE 2	27%	13%	–	–	11%	–	–
BE ACTIVE	21%	6%	3%	9%	9%	9%	52%
DISCOVER 1	24%	10%	7%	17%	13%	10%	–
FUTURE 2	16%	6%	2%	19%	10%	–	–

Abbreviations: ACR, American College of Rheumatology; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; TNFi-CI, tumour necrosis factor alpha-contra indicated.

Table 4: Mixed population, safety outcomes, baseline risk – placebo response rate

Study	SAE rate	Discontinuation rate	Discontinuation due to AE rate
ACTIVE	5%	–	5%
ADEPT	4%	8%	1%
AMVISION-1	3%	–	4%
AMVISION-2	3%	–	4%
ASTRAEA	4%	–	1%
BE ACTIVE	2%	2%	5%
BE COMPLETE	1%	6%	1%
BE OPTIMAL	1%	4%	1%
CHOICE	4%	12%	2%
COSMOS	3%	8%	2%
DISCOVER 1	4%	10%	2%
DISCOVER 2	3%	2%	2%
FUTURE 2	2%	–	4%
FUTURE 3	7%	6%	4%
FUTURE 4	–	–	1%
FUTURE 5	4%	6%	2%
GO-REVEAL	6%	9%	4%
GO-VIBRANT	3%	–	1%
IMPACT	2%	4%	2%
IMPACT 2	6%	8%	1%
KEEPsAKE 1	4%	3%	1%

Study	SAE rate	Discontinuation rate	Discontinuation due to AE rate
KEEPsAKE 2	5%	9%	1%
M02-570 Study	4%	6%	4%
MAXIMISE	2%	–	1%
NCT00317499	4%	31%	1%
NCT02719171	5%	–	–
OPAL Beyond	2%	–	4%
OPAL Broaden	1%	–	1%
PALACE 1	4%	11%	5%
PALACE 2	2%	10%	2%
PALACE 3	5%	14%	6%
PSUMMIT 1	2%	8%	3%
PSUMMIT 2	6%	23%	11%
RAPID-PsA	5%	11%	1%
Select-PSA-1	3%	16%	3%
Select-PSA-2	2%	34%	5%
SPIRIT-P1	2%	14%	2%
SPIRIT-P2	3%	20%	5%
University of Washington (Seattle, USA)	6%	16%	–

Abbreviations: AE, adverse event; SAE, serious adverse event.

A5. Priority question: The CS presents univariate fixed-effect and random-effect Bayesian NMAs (CS B.3.9.3.1). The reference 'UCB data on file CONFIDENTIAL Bimekizumab PsA efficacy NMA report 2023.pdf' indicates that

The submitted analyses adhered to established guidelines, previous NMAs, and technology appraisals by conducting and presenting analyses using both types of models. Univariate models, which present NMA results per endpoint cut-off (e.g., American College of Rheumatology 20 [ACR20], Psoriasis Area and Severity Index 75 [PASI75], etc.), were considered more robust for the base case, as multinomial models could be influenced or biased by the amount of missing data for specific treatments on certain endpoint cut-offs (e.g., missing PASI50, ACR70, etc.).

However, it is important to note that both univariate and multinomial models demonstrated that bimekizumab provides at least equal or greater efficacy compared with ixekizumab for skin outcomes (PASI) and joint outcomes (ACR). Results of the multivariate analyses are available in the separate NMA reports included in the reference pack (1, 2).

A6. The reference 'UCB data on file CONFIDENTIAL Bimekizumab PsA efficacy NMA report 2023.pdf' indicates that

The Grubbs' test is a test used to detect a single outlier in a univariate data set that follows an approximately normal distribution. The Grubbs test is defined for hypothesis by:

$$H_0: there\ is\ not\ outliers\ in\ the\ data - set$$

$$H_a: there\ is\ exactly\ one\ outlier\ in\ the\ data - set$$

The test statistics is defined as:

$$G = \frac{\max\ |Y_i - \bar{Y}|}{s}$$

With $\bar{Y}$ the sample mean and s the standard deviation of the sample. The aim of the Grubbs' test is to identify if the maximum or minimum values across the baseline characteristics is an outlier

based on the rest of the data. However, it is important to exercise caution when interpreting the results of the Grubbs' test, as it relies on the assumption of normality in the data. Therefore, before excluding any study based on the identification of a single baseline characteristic as an outlier, it is crucial to consider the limitations and potential implications of such exclusion.

The Grubbs' test was conducted on each baseline characteristics investigated in the heterogeneity assessment (Table 5).

Table 5: Grubbs' tests

Mean	SD	Study with the highest distance from the mean	G-statistic	p-value
Age				
[redacted]				
Sex				
[redacted]				
Race				
[redacted]				
[redacted]				
Mean time since diagnosis – years				
[redacted]				
Concomitant use of methotrexate – % of patients				
[redacted]				
Concomitant use of NSAIDs – % of patients				
[redacted]				
Concomitant use of steroids – % of patients				
[redacted]				
PASI score at baseline				
[redacted]				
Disease activity score in 28 Joints				
[redacted]				

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

Although between-study heterogeneity was observed, no individual study or specific group of studies could be identified as the primary source of this heterogeneity.

Study selection

A7. CS Appendix D Table 22 lists the eligibility criteria for the May 2022 and January 2023 systematic literature review updates. Bimekizumab and ixekizumab are listed as interventions of interest, and the eligible comparators are 'standard of care (e.g., cDMARDS, NSAIDs and methotrexate)' and 'placebo'. Please clarify whether these eligibility criteria would potentially

capture any head-to-head studies directly comparing bimekizumab to ixekizumab

Yes, these eligibility criteria would capture any head-to-head studies directly comparing bimekizumab and ixekizumab. As ixekizumab is approved and reimbursed for the treatment of PsA in patients who have lost response to or have a contraindication to TNFi, ixekizumab would be considered the standard of care in the comparator arm. However, no studies comparing bimekizumab with ixekizumab were identified in this SLR.

Section B: Clarification on cost-effectiveness data

Modelled population

B1. Please state what proportion of patients in the company trials had coexistent moderate to severe plaque PSO. Comment whether this proportion is likely to be representative of UK clinical practice.

Previous technology appraisals in PsA, including TA537 (5), have defined moderate to severe psoriasis (PSO) as body surface area (BSA) >3% affected by PSO and PASI score >10. The proportion of patients with BSA ≥3% affected by PSO at baseline in BE COMPLETE and BE OPTIMAL is provided in Document B, Table 11. In total, 66% of patients in BE COMPLETE, and 50% of patients in BE OPTIMAL had ≥3% BSA affected by PSO at baseline.

There is no clear-cut source for the proportion of patients with PsA in UK clinical practice that have moderate to severe PsO. UCB reviewed the publication list of the British Society for Rheumatology (BSR) biologics and biosimilars registers and identified no studies that provided information on concomitant PSO severity at baseline (6). A UK real-world evidence (RWE) study identified by UCB (n=141 patients) did not report the proportion with moderate to severe PSO (7).

In the BSR 2022 guidelines, the guideline group agreed that PSO tends to be less severe in rheumatology clinics (8), that is, patients with moderate to severe PSO would typically be more likely to be managed by dermatologist or multi-disciplinary teams with treatments prescribed based on PSO guidelines. The GRAPPA guidelines also recommend that when choosing treatments for patients with concomitant PSO, head-to-head PSO trial evidence should be considered (9).

Treatment dosing and costs

B2. CS Table 2 states "For overweight patients with plaque PSO ([including PsA with coexistent moderate to severe PSO] body weight ≥120 kg) who did not achieve complete skin clearance at Week 16, 320 mg Q4W after Week 16 may further improve treatment response." Are patients weighing ≥ 120 kg with PsA expected to increase their dose similarly if there is an insufficient response after 16 weeks? If so, what percentage of patients with PsA are expected to require this higher dose?

No dose increase is licensed for overweight patients (body weight ≥120 kg) with PsA, however the license states overweight patients with PsA with coexistent moderate to severe PSO may increase their dose if there is an insufficient response after 16 weeks (Appendix C). The dose increase for these patients is already covered by TA723 for bimekizumab for treating moderate to severe plaque psoriasis in which ixekizumab was one of the three comparators (10). As noted in TA723 (11), the proportion of the moderate to severe PSO population weighing above 120 kg is expected to be small with no substantial impact on cost comparisons.

B3. The loading dose for ixekizumab costs £2,250 (for two 80mg units @ £1,125 each; CS Table 32). However, in the model (CCM – calculations worksheet), the loading dose costs £2,812.25 in total (column V – undiscounted costs; and Z6). Please explain this discrepancy.

The model incorrectly calculated the number of cycles that the loading dose of ixekizumab is applied for. Accounting for the corrected calculations, bimekizumab (patient access scheme [PAS] price) is associated with cost-savings of [redacted] and [redacted] vs. ixekizumab in the b/tsDMARD-experienced and TNFi-CI populations, respectively, over a 10-year time horizon (Table 7 and Table 8). Results of scenario analyses in the b/tsDMARD-experienced, and TNFi-CI populations are reported in Table 9 and Table 10, respectively. After correcting the model calculations, bimekizumab, when provided at the PAS price, is still associated with cost-savings relative to list price ixekizumab in both the base-case analysis and all considered scenario analyses. A summary of results using the list price for bimekizumab is provided in Appendix B. The corrected models are provided with the response.

Table 7: 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]

Abbreviations: b/tsDMARD, biologic/targeted synthetic disease-modifying anti-rheumatic drug; PAS, patient access scheme.

Table 8: 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]

Abbreviations: PAS, patient access scheme; TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated.

Table 9: Scenario analyses: b/tsDMARD-experienced – using bimekizumab PAS price

Scenario	Difference in incremental cost	% difference
Base case	[redacted]	[redacted]
5-year time horizon	[redacted]	[redacted]
1.5% discount rate for costs	[redacted]	[redacted]
3.5% discount rate for costs	[redacted]	[redacted]
IXE PsARC response rate	[redacted]	[redacted]
No SMR adjustment	[redacted]	[redacted]
IXE 20-week PsARC response assessment	[redacted]	[redacted]

Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; IXE, ixekizumab; PAS, patient access scheme; PsARC, Psoriatic Arthritis Response Criteria; SMR, standardised mortality ratio.

Table 10: Scenario analyses: TNFi-CI – using bimekizumab PAS price

Scenario	Difference in incremental cost	% difference
Base-case	[redacted]	[redacted]
5-year time horizon	[redacted]	[redacted]
1.5% discount rate for costs	[redacted]	[redacted]
3.5% discount rate for costs	[redacted]	[redacted]
IXE PsARC response rate	[redacted]	[redacted]
PsARC response rate from the b/tsDMARD-naïve NMA (0.75)	[redacted]	[redacted]
No SMR adjustment	[redacted]	[redacted]
IXE 20-week PsARC response assessment	[redacted]	[redacted]

Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; IXE, ixekizumab; NMA, network meta-analysis; PAS, patient access scheme; PsARC, Psoriatic Arthritis Response Criteria; SMR, standardised mortality ratio; TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated.

Scenario analyses

B4. CS Section B.4.4.1 Table 38. We believe the value used in the model for the 'PsARC response rate from the b/ts DMARD naïve NMA' scenario is 0.75. Please would the company confirm if this is correct or not and state where in the CS or Appendix D this value can be found, as this efficacy option is not provided in the model.

The PsARC response rate for bimekizumab from the b/tsDMARD-naïve NMA used in a scenario analysis is 0.75. This is not reported in the Company Submission (CS) or Appendix D, however,

can be found in the 'UCB data on file CONFIDENTIAL Bimekizumab PsA efficacy NMA Report 2023' included in the reference pack. The model fit statistics and probability of achieving PsARC are provided in Table 11 and Table 12, respectively.

Table 11: Model fit statistics; b/tsDMARD-naïve population

	Adjusted				Unadjusted	
	FE		RE		FE	RE
	DIC	Beta (95% CrI)	DIC	Beta (95% CrI)	DIC	DIC
PsARC	276.62	–0.37 (–0.66, 0.02)	235.27	–0.42 (–1.06, 0.21)	283.56	**272.27**

The preferred model is in bold.
Abbreviations: b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; CrI, credible interval; DIC, deviance information criterion; FE, fixed effects; PsARC, psoriatic arthritis response criteria; RE, random effects.

Table 12: Probability of achieving PsARC; b/tsDMARD-naïve population (RE unadjusted model)

BKZ 160 mg vs IXE 80 mg Q4W	OR (95% CrI)	Probability of achieving PsARC
BKZ	–	**0.75** (0.64, 0.84)
IXE	1.53 (0.63, 3.59)	0.67 (0.50, 0.80)

Abbreviations: BKZ, bimekizumab; b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; CrI, credible interval; IXE, ixekizumab; OR, odds ratio; PsARC, psoriatic arthritis response criteria; RE, random effects.

References

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Appendix A: JAGS code

Binomial models

JAGS models

Binomial fixed effect, placebo-adjusted

```
model{
  for(i in 1:N){
    OutcomeNMA[i] ~ dbin(p[i],n[i])
    logit(p[i])<-mu[nstudy[i]]+ lorr[i]*(step(-0.1 + ntreat[i]-nb[i]))

    delta[i] <- dd[ntreat[i]] - dd[nb[i]]
    lorr[i] <- delta[i]
    +(BetaP[ntreat[i]] - BetaP[nb[i]])*(mu[nstudy[i]]-meanmu)

    #Deviance residuals for data i
    rhat[i] <- p[i] * n[i]
    dev[i] <- 2 * (OutcomeNMA[i] * (log(OutcomeNMA[i])-log(rhat[i]))  +  (n[i]-OutcomeNMA[i]) *
(log(n[i]-OutcomeNMA[i]) - log(n[i]-rhat[i])))
  }
  sumdev <- sum(dev[])

  BetaPlac ~ dnorm(0.0,0.0001)
  BetaP[1]<- 0
```

```
for (k in 2:NbTreat) {
  BetaP[k]<-BetaPlac
}


###Priors for unconstrained baseline effect (study-specific baselines)
for (j in 1:NbStudy) {
  mu[j] ~ dnorm(0.0,0.0001)
}

###Priors for basic effects (differences) parameters
dd[1]<-0
for (k in 2:NbTreat){
  dd[k] ~ dnorm(0,0.0001)
}

###Absolute log odds on Treatment A based on trials in which it was used
for (i in 1:N){
  mu_w[i] <- exp(mu[nstudy[i]])/(1+exp(mu[nstudy[i]]))*n[i]*(step(ntreat[i]-1))*(step(1-ntreat[i]))

  raw_w[i] <- (step(ntreat[i]-1))*(step(1-ntreat[i]))
  raw_w2[i] <-OutcomeNMA[i]*raw_w[i]
  tot_w[i] <- n[i]*(step(ntreat[i]-1))*(step(1-ntreat[i]))
```

```
  }

  m<- logit(sum(mu_w[])/sum(tot_w[]))

  ###Calculate treatment effects, TT[k], on natural scale
  for (k in 1:NbTreat){logit(TT[k]) <- m + dd[k]}

}
```

Binomial fixed effect unadjusted

```
model{
  for(i in 1:N){
    OutcomeNMA[i] ~ dbin(p[i],n[i])
    logit(p[i])<-mu[nstudy[i]]+ lorr[i]*(step(-0.1 + ntreat[i]-nb[i]))

    delta[i] <- dd[ntreat[i]] - dd[nb[i]]
    lorr[i] <- delta[i]

    #Deviance residuals for data i
    rhat[i] <- p[i] * n[i]
    dev[i] <- 2 * (OutcomeNMA[i] * (log(OutcomeNMA[i])-log(rhat[i]))  +  (n[i]-OutcomeNMA[i]) *
(log(n[i]-OutcomeNMA[i]) - log(n[i]-rhat[i])))
  }
  sumdev <- sum(dev[])
```

```
###Priors for unconstrained baseline effect (study-specific baselines)
for (j in 1:NbStudy) {
  mu[j] ~ dnorm(0.0,0.0001)
}

###Priors for basic effects (differences) parameters
dd[1]<-0
for (k in 2:NbTreat){
  dd[k] ~ dnorm(0,0.0001)
}

###Absolute log odds on Treatment A based on trials in which it was used
for (i in 1:N){
  mu_w[i] <- exp(mu[nstudy[i]])/(1+exp(mu[nstudy[i]]))*n[i]*(step(ntreat[i]-1))*(step(1-ntreat[i]))

  raw_w[i] <- (step(ntreat[i]-1))*(step(1-ntreat[i]))
  raw_w2[i] <-OutcomeNMA[i]*raw_w[i]
  tot_w[i] <- n[i]*(step(ntreat[i]-1))*(step(1-ntreat[i]))

}

m<- logit(sum(mu_w[])/sum(tot_w[]))
```

```
  ###Calculate treatment effects, TT[k], on natural scale
  for (k in 1:NbTreat){logit(TT[k]) <- m + dd[k]}

}
```

Binomial, random effect, placebo-adjusted

```
###Random effects model for multi-arm trials (any number of arms)
model{
  for(i in 1:NbStudy){
    w[i,1] <-0
    delta[i,1]<-0
    for (k in 1:na[i])  {
      OutcomeNMA[i,k] ~ dbin(p[i,k],n[i,k])
                                                                                #!
binomial likelihood
      logit(p[i,k])<-mu[i] + delta[i,k]
      +(BetaP[ntreat[i,k]] - BetaP[ntreat[i,1]])*(mu[i]-meanmu)

      #Deviance residuals for data i
      rhat[i,k] <- p[i,k] * n[i,k]
      dev[i,k] <- 2 * (OutcomeNMA[i,k] * (log(OutcomeNMA[i,k])-log(rhat[i,k]))  +  (n[i,k]-
OutcomeNMA[i,k]) * (log(n[i,k]-OutcomeNMA[i,k]) - log(n[i,k]-rhat[i,k])))
    }
```

```
    for (k in 2:na[i]) {
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
                                                          #! trial-specific LOR
distributions
      md[i,k] <-  dd[ntreat[i,k]] - dd[ntreat[i,1]]  + sw[i,k]
                                                      #! mean of LOR distributions
      taud[i,k] <- prec*2*(k-1)/k
                                                  #! precision of LOR distributions
      w[i,k] <- (delta[i,k]  - dd[ntreat[i,k]] + dd[ntreat[i,1]])
                                                      #! adjustment, multi-arm RCTs
      sw[i,k] <-sum(w[i,1:(k-1)])/(k-1)
                                                                          #!
cumulative adjustment for multi-arm trials
    }
    devrsum[i]<-sum(dev[i,1:na[i]])

  }
  sumdev<-sum(devrsum[])

  BetaPlac ~ dnorm(0.0,0.0001)
  BetaP[1]<- 0

  for (k in 2:NbTreat) {
    BetaP[k]<-BetaPlac
  }
```

```
###Priors for basic effects (differences) parameters

dd[1]<-0

for (k in 2:NbTreat){

  dd[k] ~ dnorm(0,0.0001)

}


tau2<-1/prec

tau<-sqrt(tau2)


#PREDICTION INTERVALS

#PredInt predi[1] <- 0

#PredInt for(k in 2:19) {

#PredInt         predi[k]~dnorm(dd[k], prec)

#PredInt }


###Prior for between-study precision/sd:

#Uniform

prec <- 1/(sd*sd)

sd ~ dunif(0.001,0.4)


###Priors for unconstrained baseline effect (study-specific baselines)

for (j in 1:NbStudy) {

  mu[j] ~ dnorm(0.0,0.0001)
```

```
  }

###Absolute log odds on Treatment A based on trials in which it was used
for (i in 1:NbStudy){
        mu_w[i] <- exp(mu[i])/(1+exp(mu[i]))*n[i,1]*(step(ntreat[i,1]-1))*(step(1-ntreat[i,1]))

        raw_w[i] <- (OutcomeNMA[i,1])*(step(ntreat[i,1]-1))*(step(1-ntreat[i,1]))

        tot_w[i] <- n[i,1]*(step(ntreat[i,1]-1))*(step(1-ntreat[i,1]))

    }
m<- logit(sum(mu_w[])/sum(tot_w[]))

  ###Calculate treatment effects, TT[k], on natural scale
 for (k in 1:NbTreat){logit(TT[k]) <- m + dd[k]}

}
```

Binomial, random-effect, unadjusted

```
###Random effects model for multi-arm trials (any number of arms)
model{
  for(i in 1:NbStudy){
    w[i,1] <-0
    delta[i,1]<-0
```

```
    for (k in 1:na[i])  {
      OutcomeNMA[i,k] ~ dbin(p[i,k],n[i,k])
                                                                                #!
binomial likelihood
      logit(p[i,k])<-mu[i] + delta[i,k]

      #Deviance residuals for data i
      rhat[i,k] <- p[i,k] * n[i,k]
      dev[i,k] <- 2 * (OutcomeNMA[i,k] * (log(OutcomeNMA[i,k])-log(rhat[i,k]))  +  (n[i,k]-
OutcomeNMA[i,k]) * (log(n[i,k]-OutcomeNMA[i,k]) - log(n[i,k]-rhat[i,k])))
    }

    for (k in 2:na[i]) {
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
                                                                #! trial-specific LOR
distributions
      md[i,k] <-  dd[ntreat[i,k]] - dd[ntreat[i,1]]  + sw[i,k]
                                                        #! mean of LOR distributions
      taud[i,k] <- prec*2*(k-1)/k
                                                #! precision of LOR distributions
      w[i,k] <- (delta[i,k]  - dd[ntreat[i,k]] + dd[ntreat[i,1]])
                                                        #! adjustment, multi-arm RCTs
      sw[i,k] <-sum(w[i,1:(k-1)])/(k-1)
                                                                                #!
cumulative adjustment for multi-arm trials
    }
```

```
  devrsum[i]<-sum(dev[i,1:na[i]])


}
sumdev<-sum(devrsum[])



###Priors for basic effects (differences) parameters
dd[1]<-0
for (k in 2:NbTreat){
  dd[k] ~ dnorm(0,0.0001)
}

tau2<-1/prec
tau<-sqrt(tau2)

#PREDICTION INTERVALS
#PredInt predi[1] <- 0
#PredInt for(k in 2:19) {
#PredInt        predi[k]~dnorm(dd[k], prec)
#PredInt }

###Prior for between-study precision/sd:
#Uniform
```

```
  prec <- 1/(sd*sd)
  sd ~ dunif(0.001,0.4)

  ###Priors for unconstrained baseline effect (study-specific baselines)
  for (j in 1:NbStudy) {
    mu[j] ~ dnorm(0.0,0.0001)
  }

###Absolute log odds on Treatment A based on trials in which it was used
for (i in 1:NbStudy){
        mu_w[i] <- exp(mu[i])/(1+exp(mu[i]))*n[i,1]*(step(ntreat[i,1]-1))*(step(1-ntreat[i,1]))

        raw_w[i] <- (OutcomeNMA[i,1])*(step(ntreat[i,1]-1))*(step(1-ntreat[i,1]))

        tot_w[i] <- n[i,1]*(step(ntreat[i,1]-1))*(step(1-ntreat[i,1]))

    }
m<- logit(sum(mu_w[])/sum(tot_w[]))

  ###Calculate treatment effects, TT[k], on natural scale
 for (k in 1:NbTreat){logit(TT[k]) <- m + dd[k]}

}
```

Continuous models

JAGS models

Continuous fixed effect, placebo-adjusted

```
model {
  for (i in 1:N) {
    prec.OutcomeNMA[i] <- 1/OutcomeNMA.var[i]
    OutcomeNMA[i]~dnorm(theta[i],prec.OutcomeNMA[i])
    theta[i] <- mu[nstudy[i]] + mdd[i]*(step(-0.1 + ntreat[i]-nb[i]))
    delta[i] <- dd[ntreat[i]] - dd[nb[i]]
mdd[i] <- delta[i]
+(BetaP[ntreat[i]] - BetaP[nb[i]])*(mu[nstudy[i]]-mean_mu)
    dev[i] <- (OutcomeNMA[i]-theta[i])* (OutcomeNMA[i]-theta[i])*prec.OutcomeNMA[i]
                                                                    #! Residual
Deviance for data i
  }
  sumdev <- sum(dev[])

  BetaPlac ~ dnorm(0.0,0.0001)
  BetaP[1]<- 0

  for (k in 2:NbTreat) {
    BetaP[k]<-BetaPlac
  }
```

```
###Priors for unconstrained baseline effect (study-specific baselines)
for (j in 1:NbStudy) {
  mu[j] ~ dnorm(0.0,0.0001)
}

###Priors for basic effects (differences) parameters
dd[1]<-0
for (k in 2:NbTreat){
  dd[k] ~ dnorm(0,0.0001)
}

###Absolute mean for Treatment A based on trials in which it was used
for (i in 1: N){
  mu_w[i] <- mu[nstudy[i]]*n[i]*(step(ntreat[i]-1))*(step(1-ntreat[i]))

  raw_w[i] <- (OutcomeNMA[i]*n[i])*(step(ntreat[i]-1))*(step(1-ntreat[i]))
  tot_w[i] <- n[i]*(step(ntreat[i]-1))*(step(1-ntreat[i]))
}
m<- sum(mu_w[])/sum(tot_w[])

meanmu <- sum(raw_w[])/sum(tot_w[])
        #! Weighted mean
```

```
###Calculate treatment effects, TT[k], on natural scale

for (k in 1:NbTreat){TT[k] <- m + dd[k])


###Rank the treatment effects (with 1=best) & record the best treatment

#  for(k in 1:10) {

#    rkk[k]<- 10+1 - rank(TT[],k)

         #! Used when best = highest

#    bestt[k]<-step(1.1 - rkk[k])

#    for (j in 1:10) {

#      preeffect[j,k]<- equals(k,rkk[j])

#    }

#  }


#  for (w in 1:10){

#    T[pretreat[w]]<-TT[w]

#    best[pretreat[w]]<-bestt[w]

#    d[pretreat[w]]<-dd[w]

#    rk[pretreat[w]]<-rkk[w]

#  }


#  for (index in 1:10){

#    study[prestudy[index]]<-mu[index]

#  }
```

```
 #  for (c in 1:NbTreat){
 #    for (k in 1:10){
 #      effectiveness[c,pretreat[k]]<- preeffect[c,k]
 #    }
 #  }

 ###All pairwise comparisons, we had 9 as the 10 treatment is already compared
# for (c in 1:(NbTreat-1)){
 #   for (k in (c+1):NbTreat){
 #     meandif[pretreat[c],pretreat[k]] <- dd[k] - dd[c]
 #     meandifprob[pretreat[c],pretreat[k]] <- step(meandif[pretreat[c],pretreat[k]])
 #     RateRatio[pretreat[c],pretreat[k]] <- exp(meandif[pretreat[c],pretreat[k]])
 #   }
 # }


}
```

Continuous model, fixed-effect, unadjusted

```
model {
  for (i in 1:N) {
    prec.OutcomeNMA[i] <- 1/OutcomeNMA.var[i]
    OutcomeNMA[i]~dnorm(theta[i],prec.OutcomeNMA[i])
    theta[i] <- mu[nstudy[i]] + mdd[i]*(step(-0.1 + ntreat[i]-nb[i]))
```

```
  delta[i] <- dd[ntreat[i]] - dd[nb[i]]

  mdd[i] <- delta[i]

  dev[i] <- (OutcomeNMA[i]-theta[i])* (OutcomeNMA[i]-theta[i])*prec.OutcomeNMA[i]
                                                                    #! Residual
Deviance for data i

 }

 sumdev <- sum(dev[])


 ###Priors for unconstrained baseline effect (study-specific baselines)

 for (j in 1:NbStudy) {

  mu[j] ~ dnorm(0.0,0.0001)

 }


 ###Priors for basic effects (differences) parameters

 dd[1]<-0

 for (k in 2:NbTreat){

  dd[k] ~ dnorm(0,0.0001)

 }


 ###Absolute mean for Treatment A based on trials in which it was used

 for (i in 1: N){

  mu_w[i] <- mu[nstudy[i]]*n[i]*(step(ntreat[i]-1))*(step(1-ntreat[i]))


  raw_w[i] <- (OutcomeNMA[i]*n[i])*(step(ntreat[i]-1))*(step(1-ntreat[i]))
```

```
  tot_w[i] <- n[i]*(step(ntreat[i]-1))*(step(1-ntreat[i]))
}
m<- sum(mu_w[])/sum(tot_w[])

meanmu <- sum(raw_w[])/sum(tot_w[])
          #! Weighted mean

###Calculate treatment effects, TT[k], on natural scale
for (k in 1:NbTreat){TT[k] <- m + dd[k]}

###Rank the treatment effects (with 1=best) & record the best treatment
#  for(k in 1:10) {
#    rkk[k]<- 10+1 - rank(TT[],k)
          #! Used when best = highest
#    bestt[k]<-step(1.1 - rkk[k])
#    for (j in 1:10) {
#      preeffect[j,k]<- equals(k,rkk[j])
#    }
#  }

#  for (w in 1:10){
#    T[pretreat[w]]<-TT[w]
#    best[pretreat[w]]<-bestt[w]
```

```
#    d[pretreat[w]]<-dd[w]
#    rk[pretreat[w]]<-rkk[w]
#  }

#  for (index in 1:10){
#    study[prestudy[index]]<-mu[index]
#  }

#  for (c in 1:NbTreat){
#    for (k in 1:10){
#      effectiveness[c,pretreat[k]]<- preeffect[c,k]
#    }
#  }

 ###All pairwise comparisons, we had 9 as the 10 treatment is already compared
# for (c in 1:(NbTreat-1)){
#   for (k in (c+1):NbTreat){
#     meandif[pretreat[c],pretreat[k]] <- dd[k] - dd[c]
#     meandifprob[pretreat[c],pretreat[k]] <- step(meandif[pretreat[c],pretreat[k]])
#     RateRatio[pretreat[c],pretreat[k]] <- exp(meandif[pretreat[c],pretreat[k]])
#   }
# }
```

```
}
```

Continuous mode, random-effect, placebo-adjusted

```
###Random effects model for multi-arm trials (any number of arms)
model{
  for(i in 1:NbStudy){
    w[i,1] <-0
    delta[i,1]<-0
    for (k in 1:na[i])  {
      prec.OutcomeNMA[i,k] <- 1/OutcomeNMA.var[i,k]
      OutcomeNMA[i,k]~dnorm(theta[i,k],prec.OutcomeNMA[i,k])
      theta[i,k]<-mu[i] + delta[i,k]
      dev[i,k] <- (OutcomeNMA[i,k]-theta[i,k])*(OutcomeNMA[i,k]-theta[i,k])*prec.OutcomeNMA[i,k]
#! Residual Deviance for data i
    }

    for (k in 2:na[i]) {
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])                                    #! trial-specific LOR
distributions
      md[i,k] <- dd[ntreat[i,k]] - dd[ntreat[i,1]] + sw[i,k]                   #! mean of LOR
distributions
      taud[i,k] <- prec*2*(k-1)/k                                              #! precision of LOR
distributions
      w[i,k] <- (delta[i,k]  - dd[ntreat[i,k]] + dd[ntreat[i,1]])
      sw[i,k] <-sum(w[i,1:(k-1)])/(k-1)                                        #! cumulative
adjustment for multi-arm trials
```

```
    }
    devrsum[i]<-sum(dev[i,1:na[i]])
  }
  sumdev<-sum(devrsum[])

  ###Priors for basic effects (differences) parameters
  dd[1]<-0
  for (k in 2:NbTreat){ dd[k] ~ dnorm(0,0.0001)
  }

  tau<-sd

  ###Prior for between-study precision/sd:
  prec <- 1/(sd*sd)                                    #! Uniform prior for
het SD
  sd ~ dunif(0.001,0.4)

  ###Priors for unconstrained baseline effect (study-specific baselines)
  for (j in 1:NbStudy) {
    mu[j] ~ dnorm(0.0,0.0001)
  }

}
```

Continuous model, random-effect, unadjusted

```
###Random effects model for multi-arm trials (any number of arms)

model{

  for(i in 1:NbStudy){

    w[i,1] <-0

    delta[i,1]<-0

    for (k in 1:na[i])  {

      prec.OutcomeNMA[i,k] <- 1/OutcomeNMA.var[i,k]

      OutcomeNMA[i,k]~dnorm(theta[i,k],prec.OutcomeNMA[i,k])

      theta[i,k]<-mu[i] + delta[i,k]

      +(BetaP[ntreat[i,k]] - BetaP[ntreat[i,1]])*(mu[i]-mean_mu)

      dev[i,k] <- (OutcomeNMA[i,k]-theta[i,k])*(OutcomeNMA[i,k]-theta[i,k])*prec.OutcomeNMA[i,k]
#! Residual Deviance for data i

    }


    for (k in 2:na[i]) {

      delta[i,k] ~ dnorm(md[i,k],taud[i,k])                                    #! trial-specific LOR
distributions

      md[i,k] <- dd[ntreat[i,k]] - dd[ntreat[i,1]] + sw[i,k]                    #! mean of LOR
distributions

      taud[i,k] <- prec*2*(k-1)/k                                              #! precision of LOR
distributions

      w[i,k] <- (delta[i,k]  - dd[ntreat[i,k]] + dd[ntreat[i,1]])

      sw[i,k] <-sum(w[i,1:(k-1)])/(k-1)                                        #! cumulative
adjustment for multi-arm trials

    }
```

```
  devrsum[i]<-sum(dev[i,1:na[i]])
 }
 sumdev<-sum(devrsum[])

 BetaPlac ~ dnorm(0.0,0.0001)
 BetaP[1]<- 0

 for (k in 2:NbTreat) {
  BetaP[k]<-BetaPlac
 }

 ###Priors for basic effects (differences) parameters
 dd[1]<-0
 for (k in 2:NbTreat){ dd[k] ~ dnorm(0,0.0001)
 }

 tau<-sd

 ###Prior for between-study precision/sd:
 prec <- 1/(sd*sd)                                    #! Uniform prior for
het SD
 sd ~ dunif(0.001,0.4)

 ###Priors for unconstrained baseline effect (study-specific baselines)
```

```
  for (j in 1:NbStudy) {
    mu[j] ~ dnorm(0.0,0.0001)
  }
}
```

Appendix B: List price results

Table 13: 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

Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug.

Table 14: 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

Abbreviations: TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated.

Table 15: Scenario analyses: b/tsDMARD-experienced – using bimekizumab list price

Scenario	Difference in incremental cost	% difference
Base case	£4,074	–
5-year time horizon	£2,608	–36%
1.5% discount rate for costs	£3,849	–6%
3.5% discount rate for costs	£3,580	–12%
IXE PsARC response rate	£3,055	–25%
No SMR adjustment	£4,077	0%
IXE 20-week PsARC response assessment	£3,127	–23%

Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; IXE, ixekizumab; PsARC, Psoriatic Arthritis Response Criteria; SMR, standardised mortality ratio.

Table 16: Scenario analyses: TNFi-CI – using bimekizumab list price

Scenario	Difference in incremental cost	% difference
Base-case	£3,970	–
5-year time horizon	£2,532	–36%
1.5% discount rate for costs	£3,749	–6%
3.5% discount rate for costs	£3,485	–12%
IXE PsARC response rate	£3,232	–19%
PsARC response rate from the b/tsDMARD-naïve NMA (0.75)	£3,516	–11%
No SMR adjustment	£3,972	0%
IXE 20-week PsARC response assessment	£3,017	–24%

Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; IXE, ixekizumab; NMA, network meta-analysis; PsARC, Psoriatic Arthritis Response Criteria; SMR, standardised mortality ratio; TNFi-CI, tumour necrosis factor alpha inhibitor-contraindicated.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal
Bimekizumab for treating active psoriatic arthritis [ID4009]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	A patient-centred charity that exists to support people affected by psoriasis and psoriatic arthritis. Activities include information both in print and via a comprehensive website. Telephone support offering help, advice and a sign-posting service to other resources is also available. The organisation also supports research via a small grants scheme. Health care professionals continued development is promoted and supported with an accredited online *Psoriasis in Practice* training resource (free to NHS staff). There is no formal membership of the organisation, but subscriptions are available to receive a bi-annual *Skin 'n' Bones Connection* journal, all other patient resources and support are free and can be accessed anonymously. Access to the website is also free, with limited sign-up details needed to enter the PAPAA *Knowledge Bank.* Use of social media is also part of the organisations activities, but with a strict policy of only publishing evidenced-based and reliably sourced content. Funding is via donations, journal subscriptions, online shop sales, fundraising activities and an ethical investment portfolio. No funds are currently accepted from commercial organisations (including the pharmaceutical industry) or third-party agents representing or supporting those sectors.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	No

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information used in this submission has been gathered and based on direct feedback from people affected by psoriatic arthritis, and my personal experience of living with psoriatic arthritis. PAPAA also has a continuing data gathering process, since 2014 via the PAPAA survey.

Current treatment of the condition in the NHS

6. Do people using the technology feel that it works in the same way as the comparator(s)?	The technology is not currently available for psoriatic arthritis within the NHS, but is recommended and prescribed for psoriasis [TA723]. Therefore, it would be difficult to access if it works the same as comparators. It is a targeted inhibitor of interleukin (IL) -17F and IL-17A. Both ixekizumab and secukinumab target those, therefore it would be reasonable to assume that bimekizumab should provide equivalent efficacy. There are also other class comparators that have different targets. It would be equally reasonable to include those indirectly in any comparison.
7. Are there any key differences?	Bimekizumab is self-administered as a sub-cutaneous injection, every 4-weeks then every 8 weeks for maintenance for psoriasis indication. Ixekizumab is the same, but maintenance is every 4-weeks, secukinumab is every week, for 5 weeks, then every month for maintenance. Long-term less frequent maintenance may be useful from a patient perspective.
8. Will this technology be easier, the same, or more difficult to take than the comparator(s)? If so, please explain why	Doesn't appear to be any more or less difficult than comparators.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	For those that have both psoriasis and psoriatic arthritis, being able to benefit both domains with a single therapy, would appear to be advantageous, less frequent maintenance dose would also be helpful for travelling and storage.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	There does not appear to be any obvious disadvantages, as delivery and adverse events are similar to same class therapies.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No different than other same class therapies.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that are obviously related to the Equality Act.

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Similar target/action to same class therapies • Could be useful for those with both psoriatic arthritis and psoriasis • Less frequent maintenance dose • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal
Bimekizumab for treating active psoriatic arthritis [ID4009]
Patient Organisation Submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Psoriasis Association
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Patient Support Organisation and Charity. The reach of the Psoriasis Association now extends much further than that of the original member. The Psoriasis Association currently has around 2000 members who help to fund the organisation via an annual fee. Other sources of income include fundraising (individuals, legacies and trusts), Gift Aid, investments and unrestricted educational grants from the Pharmaceutical Industry for projects (there is a policy that no more than 15% of the total income of the Psoriasis Association can come from the Pharmaceutical Industry). The Psoriasis Association has three main aims; to provide information advice and support, to raise awareness and to fund and promote research. In addition to traditional members, the Psoriasis Association regularly communicates with, or offers a platform enabling people whose lives are affected by the condition to communicate with one another via online forums on their own websites (~17,500 registered users), and Social Media (~7,200 registered users on closed Facebook group). The main Psoriasis Association website averages 48,000 visits per month. Other social media channels used by the Psoriasis Association that lend themselves more to “raising awareness” include Twitter (~14,000 followers) and Instagram (~12,450 followers), along with a YouTube channel offering further information. The Psoriasis Association has been passionate about research throughout its 50+ year history. Regularly funding PhD studentships, alongside supporting the PPI of bigger research collaborations (including the James Lind Alliance Top 10 Research Priorities for Psoriatic Arthritis), always seeking to improve the lives of those affected by psoriatic disease and in 2021 awarded £1 million to the Biomarkers and Stratification to Optimise outcomes in Psoriasis (BSTOP) research project based at Kings College, London.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Yes – UCB £1,500 corporate membership, £6,505 honorarium, £5,000 towards annual conference costs Abbvie – £1,500 corporate membership, £2,500 towards annual conference costs, £6,500 core funding Eli Lilly – £2,000 corporate membership, £2,500 towards annual conference costs Janssen – £1,500 corporate membership, £600 honorarium, £2,500 towards annual conference costs, £8,500 core funding Novartis – £3,009 honorarium, £2,500 towards annual conference costs Bristol Myers Squibb - £1,500 corporate membership, £380 honorarium
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	This submission has been informed by informal, anecdotal information that we hear from patients and carers themselves, through the following channels provided by the Psoriasis Association:- the Psoriasis Association website (592,912 visitors in 2022) helpline (801 enquiries in 2022) online forums (18,937 registered users in 2022) social media channels (including Facebook Group, Twitter and Instagram, 36,325 people in 2022) The Psoriasis Association analyses the data gathered from all communication channels (mentioned above) and monitors for trends in addition to interesting new requests. We have completed a Priority Setting Partnership on Psoriasis which gave valuable insight into issues affecting people living with psoriasis and supported the Priority Setting Partnership on psoriatic arthritis (including membership of the Steering Committee).

Current treatment of the condition in the NHS

6. Do people using the technology feel that it works in the same way as the comparator(s)?	Many will have tried the comparators and will be seeking a new treatment following it failing – as the treatment targets both IL-17A and IL-17F pathways it would be hoped that it works better than previous treatments. Also, patients may not have received a treatment previously that targets both the skin psoriasis and the joints (PsA) concomitantly.
7. Are there any key differences?	
8. Will this technology be easier, the same, or more difficult to take than the comparator(s)? If so, please explain why	This comes down to patient preferences and the slightly different packaging types of administering the medication and dosing regimes. For some, every four weeks would be preferable to every two weeks and easier to fit into busy lives than some of the comparators.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The technology builds on the increasing understanding of the role of IL-17 in psoriasis and psoriatic arthritis. Bimekizumab being the only existing treatment that targets the IL-17A and IL-17F pathways. As identified by the James Lind Alliance Priority Setting Partnership on Psoriatic Arthritis Top 10 Research Priorities; "why do treatments stop working well against PsA" demonstrates the frustrations of people living with PsA and the problem that there is not one treatment that works for all, or for a long period of time. It is therefore important to have as wide a treatment armamentarium as possible. A patient commented "It (PsA) takes away your life and puts you on medication forever". Therefore people need a treatment that works and can be tolerated, and fits into lifestyle (taking into account the needs of different age groups, e.g. child-bearing age). We should not overlook the dual aspects of this treatment in that it treats skin psoriasis alongside PsA. A second patient commented "arthritis is debilitating, and together with psoriasis, it has been hard to find ways of enjoying life whilst in pain and itchy". It is also important to acknowledge the life changing impacts having PsA can have, and what successful treatment means in terms of living a 'normal' life – a patient explained "Getting in and out of the car was difficult. I thought I'd have to give up my job. After trying so many tablets and treatments over a long period of time, my Rheumatology Consultant put me onto a biological therapy injection and I have not looked back since". Further advantages include better tolerability of the medication than some traditional systemic DMARDs.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	There can be apprehension when self-injecting for the first time, with some patients preferring an oral medication. However, with appropriate training many patients overcome any initial fears.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People with visible skin psoriasis alongside PsA will likely benefit from the technology as it can treat both conditions (particularly for those with high impact sites affected that do not achieve a PASI score >10).

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Depending on the considerations of the Committee as to the degree of skin psoriasis involvement when considering recommending this treatment for people with PsA, severe psoriasis in high impact sites will not result in a high (>10 PASI score) yet should still be classed as severe. The PASI is not a suitable assessment for psoriasis on high impact sites (such as the hands, feet, face and genitals). It is also not as robust a measure in black skin. The increased use of telephone or video consultations can also cause issues with assessing the severity of psoriasis (in all skin types). The continuation of treatment if the skin responds more quickly / better to the treatment than the joints.

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Untreated and under-treated psoriatic arthritis can not only destroy the joints of those affected, but the lives of those affected • Having a treatment that can work on the joints and skin is of importance to patient choice • There are currently few treatments available to treat psoriatic arthritis over the life time, and so an extension to the treatment armoury is most welcome • Having a self-administration device that can be used easily by patients affected by the condition is of great value. • Comorbidities such as fatigue, sleep disturbance, pain, diminished work capacity and social participation should be included when assessing adequate treatment response

Thank you for your time.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Bimekizumab for treating active psoriatic arthritis

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Declared competing interests of the authors and advisors

- The authors declare none.
- Dr Ho declares attending the North Rheumatology educational meeting in May 2023 which was sponsored by UCB.

Rider on responsibility for report

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

This report should be referenced as follows:

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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

Content in this report highlighted in yellow and underlined is ‘academic in confidence’.

Content underlined in blue is ‘commercial in confidence’.

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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.

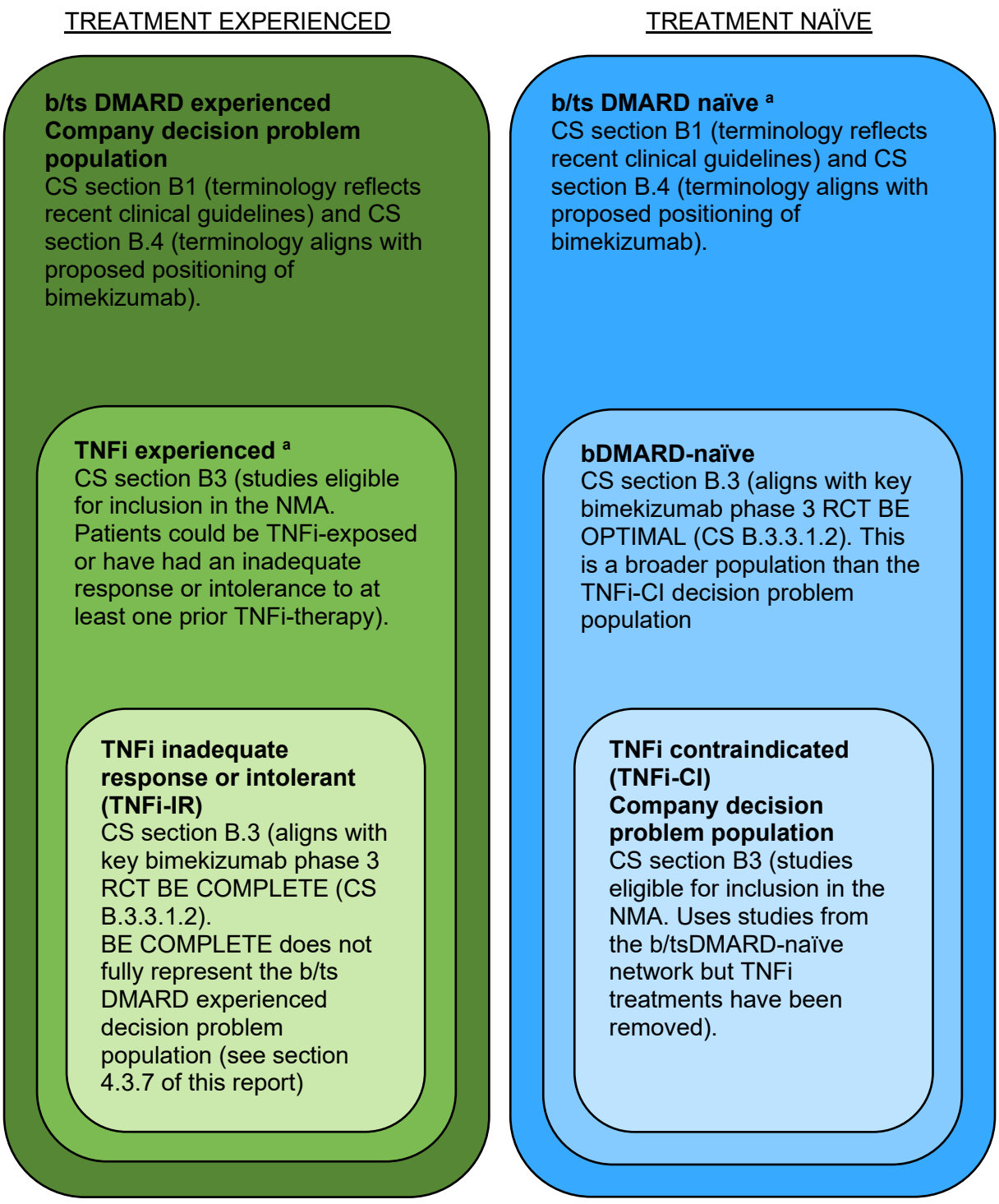

Figure 1 Terminology used to describe different population subgroups in the CS

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.

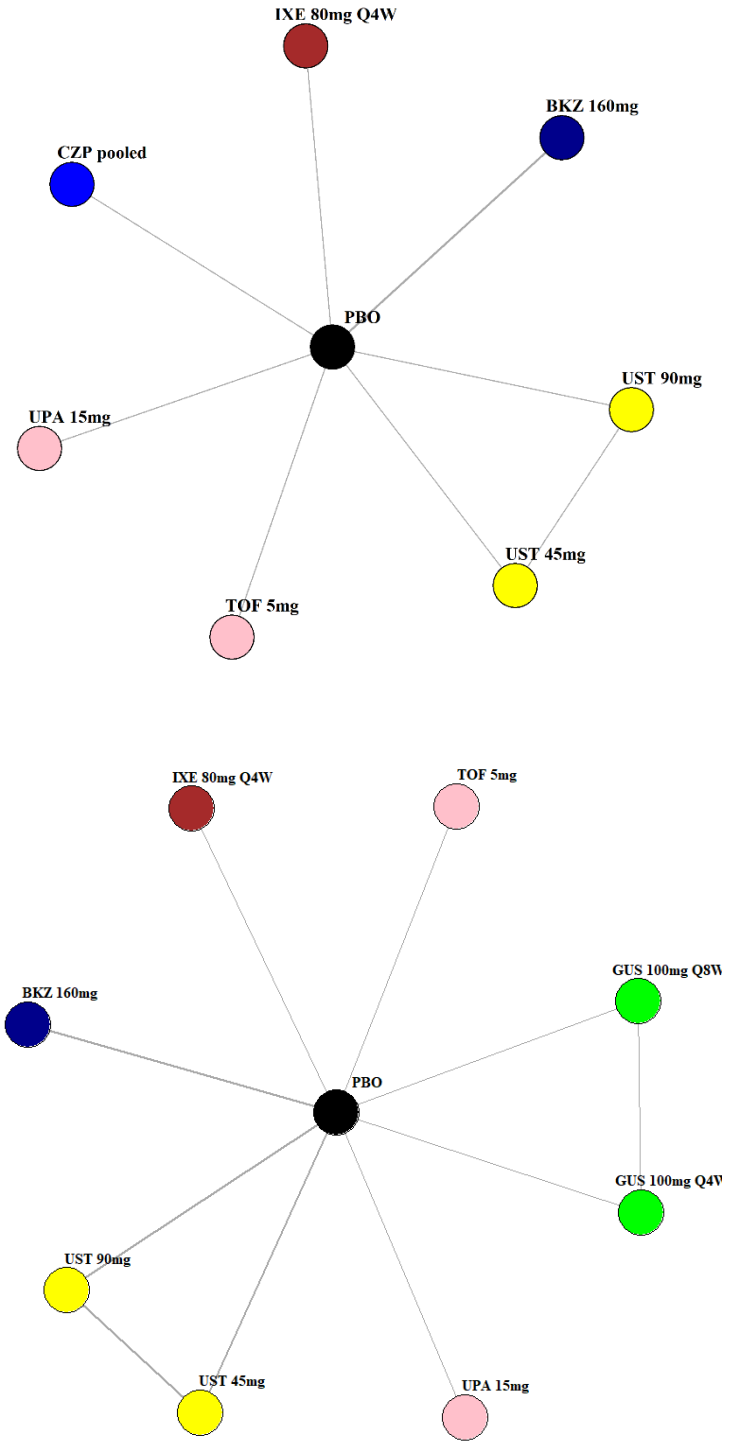

Figure 2 Network of evidence for the PsARC outcome in the TNFi-experienced population (top) and the TNF-CI population (bottom)

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

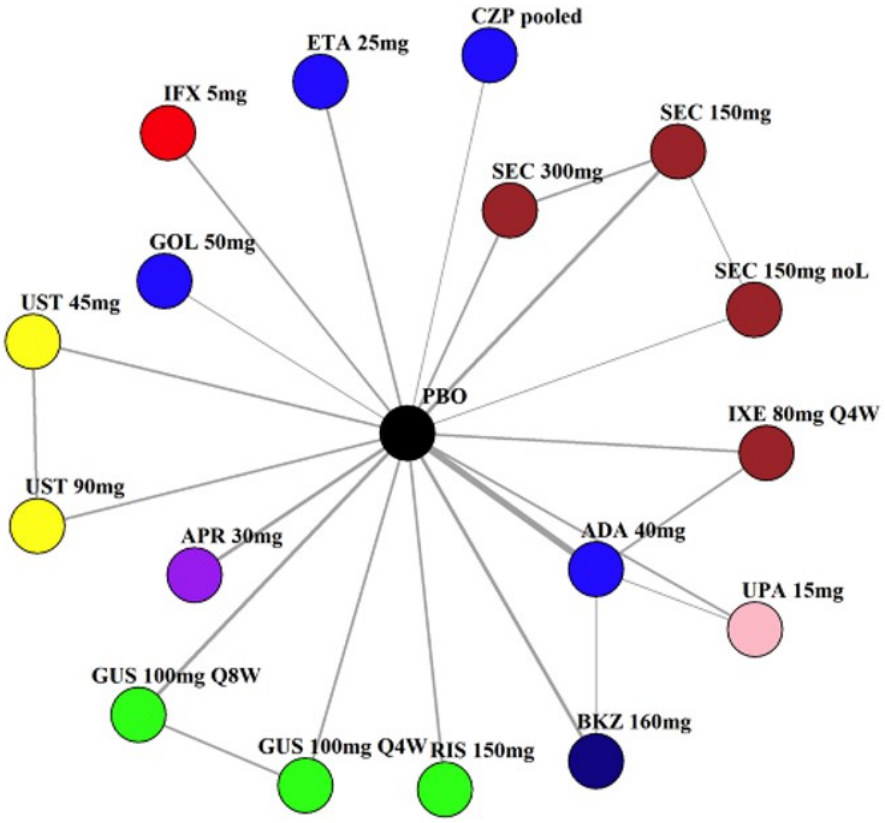

Figure 3 Network of evidence for the Discontinuation outcome in the mixed population (patients who are b/tsDMARD-naïve or TNFi-experienced)

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.

Cost Comparison Appraisal

Bimekizumab for treating active psoriatic arthritis [ID4009]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 20 July** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Clinical effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16 The EAG state: *"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*	UCB propose amending to the following: "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. RCT data demonstrates consistent sustained clinical efficacy across disease manifestations to Week 52 in bDMARD-naïve patients, irrespective of concomitant methotrexate (Reference: McInnes I, Mease PJ, Tanaka Y, Behrens F, Gossec L, Husni ME, et al. POS1537 Bimekizumab efficacy and safety in biologic DMARD-naïve patients with psoriatic arthritis was consistent with or without methotrexate: 52-week results from the phase 3 active reference study BE OPTIMAL. Abstract presented at EULAR 2023. Available at: https://ard.bmj.com/content/82/Suppl_1/1133.info (last accessed July 2023). 2023.)"	Although the use of methotrexate in combination with bimekizumab is a clinical decision, the reference clarifies that bimekizumab treatment has demonstrated consistent sustained clinical efficacy across disease manifestations to Week 52 in bDMARD-naïve patients, irrespective of concomitant methotrexate	No amendment made because this is not a factual inaccuracy or an error. Additionally, this section of the report is the critique of the decision problem which is not an appropriate place to report trial results.

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proportion was likely to reduce for clinical reasons (e.g. liver abnormalities) and patient preference for monotherapy if they are in remission."			
Page 22 The EAG state: *"The CS states that, currently, this study only provides follow-up data for BE COMPLETE."*	UCB propose to amend the sentence from: "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." to "This is an ongoing open-label extension to BE COMPLETE and BE OPTIMAL (CS section B.3.2). In the CS, results for BE COMPLETE and BE OPTIMAL are presented to Week 52; as BE COMPLETE was a 16-week study, Week 52 results were derived from BE COMPLETE patients who enrolled in BE VITAL. No data beyond Week 52 are	The proposed amendment clarifies the trials and timepoints presented in the submission	This is not a factual inaccuracy or an error, however we have made the following minor amendment for clarity. "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."

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	currently available from BE OPTIMAL or BE COMPLETE patients, however long-term efficacy, and safety evidence for bimekizumab up to 3 years is provided in BE ACTIVE and BE ACTIVE 2 (references: Coates LC, McInnes IB, Merola JF, Warren RB, Kavanaugh A, Gottlieb AB, et al. Safety and Efficacy of Bimekizumab in Patients with Active Psoriatic Arthritis: 3-Year Results from a Phase 2b Randomized Controlled Trial and its Open-Label Extension Study. Arthritis Rheumatol. 2022. **and** Mease PJ, Asahina A, Gladman DD, Tanaka Y, Tillett W, Ink B, et al. Effect of bimekizumab on symptoms and impact of disease in patients with psoriatic arthritis over 3 years: results from BE ACTIVE. Rheumatology (Oxford). 2023;62(2):617-28.)"		
Page 23 The EAG state: *"The EAG suggests, therefore, that the BE COMPLETE trial population may not fully reflect all*	UCB propose to amend the sentence from: "The EAG suggests, therefore, that the BE COMPLETE trial population may not fully reflect all patients with active psoriatic arthritis seen in clinical practice." to "The EAG suggests, therefore, that the BE COMPLETE trial population may not fully reflect all patients with active psoriatic arthritis seen in clinical	The proposed amendment clarifies that the population in BE COMPLETE is consistent with the inclusion criteria of the ixekizumab trial, SPIRIT-P2.	No amendment has been made because this is not a factual inaccuracy or an error. Additionally, BE COMPLETE and SPIRIT-P2 patients' baseline characteristics are compared in section 4.5.2.2 of the EAG report where we state "Overall, although there are some differences between the bimekizumab and ixekizumab

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patients with active psoriatic arthritis seen in clinical practice."	practice. However, the comparator trial, SPIRIT-P2, shares inclusion criteria requiring CASPAR PsA diagnosis and active or historic plaque psoriasis, so any differences with the UK population will be similar between bimekizumab and ixekizumab based on these factors."		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."
Page 25 The EAG state: "*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*	UCB propose to amend the sentence from: "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." to "As stated above regarding the BE COMPLETE trial, we suggest that the BE OPTIMAL trial population may not fully reflect all patients with	The proposed amendment clarifies that the population in BE OPTIMAL is consistent with the inclusion criteria of the ixekizumab trial, SPIRIT-P1.	Similar to the row above, no amendment has been made because this is not a factual inaccuracy or an error. Additionally, BE OPTIMAL and SPIRIT-P2 patients' baseline characteristics are compared in section 4.5.2.2 of the EAG report

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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."	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. However, the inclusion criteria are consistent with the ixekizumab SPIRIT-P1 trial, which required patients to meet CASPAR criteria for PsA diagnosis, and have active psoriatic skin lesions or a history of plaque psoriasis."		
Page 25 The EAG state: *"Participants received open-label bimekizumab and were followed up for a period of up to 140 weeks (which equates to around 2.7 years), with*	UCB propose amending the wording from: "Participants received open-label bimekizumab and were followed up for a period of up to 140 weeks (which equates to around 2.7 years), with participants from BE COMPLETE being followed up from Week 16 and those from BE OPTIMAL from Week 52." to "In the ongoing open-label extension study, 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 of 20 weeks after the final dose, which	The updated text reflects the current status of BE VITAL, which is ongoing (expected to end in 2025 with follow-up to Week 212 including the safety follow-up period).	The wording of EAG report section 4.3.3 has been amended as follows: "The characteristics of the ongoing 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] [redacted]

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participants from BE COMPLETE being followed up from Week 16 and those from BE OPTIMAL from Week 52."	equates to ~4 years), with participants from BE COMPLETE being followed up from Week 16 and those from BE OPTIMAL from Week 52. Week 52 results for BE COMPLETE from BE VITAL presented in the CS are from entry into BE COMPLETE rather than entry into BE VITAL."		

Issue 2 Cost-comparison approach

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12 The EAG state:	UCB propose removing the statement and note that the decision to use the cost-comparison approach was discussed at scoping, and at the	An explicit statement in the CS regarding the reason why bimekizumab is being considered using the cost-	Although this is not a factual inaccuracy or an error, we agree that the NICE Invitation to

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"The company does not explicitly state in the CS why bimekizumab for treating psoriatic arthritis is *being considered using the cost-comparison approach."*	decision problem meeting (where NICE and the EAG indicated that an STA CC was appropriate). In addition, an ITP for a cost-comparison was issued by NICE.	comparison approach was not included in the CS as this was addressed earlier in the submission process.	Participate was for a cost-comparison and so we have removed this sentence from our report.

Issue 3 Network meta-analysis

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Page 41: The EAG state: *"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, but this was not explicitly stated in the CS."*	UCB propose amending the following: "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, but this was not explicitly stated in the CS." to "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, as the CSR states that the randomised period ends at	The proposed amendment clarifies the rationale for using Week 12 data in the analysis.	This is not a factual inaccuracy or an error, however we have made the following minor amendment for clarity. "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

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	Week 12. As no patients received placebo after Week 12, Week 12 data is the only data that could be used in the analysis."		week 12), but this was not explicitly stated in the CS."
Page 43: The EAG state: *"The company does not present results for the multivariate NMAs (these were not conducted for every outcome)."*	UCB propose amending: "The company does not present results for the multivariate NMAs (these were not conducted for every outcome)." to "The company does not present results for the multivariate NMAs in the CS Document B or Appendix D, however results of multivariate NMAs were provided in the NMA report included in the reference pack (CS reference 194, Document B) (these were not conducted for every outcome). Results of the multivariate analyses conducted (ACR, and PASI outcomes) were similar to the univariate analyses results."	Results of the multivariate analyses were provided in the NMA report included in the reference pack.	The wording of EAG report section 4.3.3 has been amended as follows: "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)."

Issue 4 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 25 Incorrect trial name	Please amend: "The bimekizumab dose used was the same as administered in the BE VITAL and BE COMPLETE trials (160mg Q4W via SC injection)." to "The bimekizumab dose used was the same as administered in the BE OPTIMAL and BE COMPLETE trials (160mg Q4W via SC injection)."	Trial name amended for accuracy.	This typographical error has been corrected.
Page 50 Incorrect list price for bimekizumab	Please amend: "List price £1,125.50" to "List price £1,221.50"	The proposed amended list price for bimekizumab matches the value provided in the CS Table 32, Document B.	This typographical error has been corrected.

Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, page 25	Participants received open-label bimekizumab and were followed up for a period of up to 140 weeks (which equates to around 2.7 years), with participants from BE COMPLETE being followed up from Week 16 and those from BE OPTIMAL from Week 52. The bimekizumab dose used was the same as administered in the BE VITAL and BE COMPLETE trials (160mg Q4W via SC injection).	Please unmark and amend as above	The AIC marking for this text has been removed
EAG report, page 67	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.	Please unmark	The AIC marking for this text has been removed
EAG report, page 67	**BE ACTIVE:** Study sites were expected to have a plan in place to maintain the	Please unmark	The AIC marking for this text has been removed

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	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]		
EAG report, page 68–69	**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 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]	Please unmark	The AIC marking for this text has been removed

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	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]		