NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bimekizumab for treating axial spondyloarthritis [ID6245]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Bimekizumab for treating axial spondyloarthritis [ID6245]

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. British Society for Rheumatology
   b. National Axial Spondyloarthritis Society

4. **External Assessment Report** prepared by York

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

Single technology appraisal

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Document B

Company evidence submission

File name	Version	Contains confidential information	Date
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Abbreviations

Acronym	Definition
AE	Adverse event
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASASX	Assessment of SpondyloArthritis international Society X% response
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
AxSpA	Axial spondyloarthritis
b/tsDMARD	Biologic/targeted synthetic disease modifying anti-rheumatic drug
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASDAI50	Bath Ankylosing Spondylitis Disease Activity Index 50% response
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BHPR	British Health Professionals in Rheumatology
BSR	British Society of Rheumatology
CfB	Change from baseline
CI	Confidence interval
CrI	Credible interval
CRP	C-reactive protein
DSU	Decision Support Unit
EAIR	Exposure-adjusted incidence rate
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
HR	Hazard ratio
HRQoL	Health-related quality-of-life
HS	Hidradenitis suppurativa
IBD	Inflammatory bowel disease
IL	Interleukin
IQR	Interquartile range
ITC	Indirect treatment comparison
JAK	Janus kinase
MACE	Major adverse cardia event
MAIT	Mucosal associated invariant T
MI	Major improvement
mNY	Modified New York
MRI	Magnetic resonance imaging
NASS	National Axial Spondyloarthritis Society
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
Nr-axSpA	Non-radiographic axial spondyloarthritis

Acronym	Definition
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient access scheme
PR	Partial remission
PRO	Patient-reported outcomes
PsA	Psoriatic arthritis
PSO	Psoriasis
PtGA	Patients Global Assessment of Disease Activity
PY	Patient year
QoL	Quality of life
QXW	Every X weeks
R-axSpA	Radiographic axial spondyloarthritis
RCT	Randomised controlled trial
SAE	Serious adverse event
SIJ	Sacroiliac joint
SLR	Systematic literature review
SmPC	Summary of product characteristics
SPARCC	Spondyloarthritis Research Consortium of Canada
TNF-α	Tumour necrosis factor alpha
UK	United Kingdom
US	United States
VAS	Visual analogue scale

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

Axial spondyloarthritis (axSpA) is a chronic, progressive systemic inflammatory condition affecting the spine and sacroiliac joints (SIJ). It encompasses two subtypes dependent on the degree of structural damage of the SIJ on x-rays; non-radiographic axSpA (nr-axSpA) and radiographic axSpA (r-axSpA; also known as ankylosing spondylitis [AS]) (1-10) (Section B.1.3).

- Nr-axSpA is characterised by the absence of definitive radiographic evidence of structural damage (but with signs of objective inflammation), while patients with AS present with radiographic damage of the SIJ (1-3). Disease onset is typically mid-twenties, with median age at onset of axial symptoms ~26 years (4).
- An estimated 10–40% of patients with nr-axSpA progress to AS over 2–10 years, and 60% of patient progress during their lifetime (5, 6, 11).
- There is a lack of reliable prevalence data for axSpA, partly because there is an average delay in diagnosis of 8.5 years (7, 8), with longer delays in females than males as females are often misdiagnosed . Overall, axSpA is estimated to affect 1 in 200 (0.5%) patients in the United Kingdom (UK) (8). Only one study provides prevalence estimates for nr-axSpA, reporting an nr-axSpA prevalence of 0.35%, and an equivalent AS prevalence of 0.35% in the United States (US) (12).

AxSpA is associated with a considerable clinical, humanistic, and economic burden (1-3, 13-29) (Section B.1.3.3).

- The burden is similar for nr-axSpA and AS, and if left uncontrolled can lead to irreversible axial, structural damage (1-3, 13-16).
- The main symptoms of axSpA are chronic back pain, stiffness, and fatigue, which affect the ability to perform activities of daily living (17, 18).
- Over the lifelong course of disease, many patients experience peripheral manifestations (in joints other than the spine or SIJ), the most common of which are peripheral arthritis and enthesitis (affecting an estimated 28–57% and 37–74% of patients, respectively) (19) (1, 30). Patients also experience extra-articular manifestations, including uveitis, psoriasis, and inflammatory bowel disease (IBD) which also increase over the course of disease (18, 20-22).
- The symptoms of axSpA can significantly impact patient health-related quality of life (HRQoL) (23, 24), and often also result in fatigue, distress, depression, and anxiety (25-28).
- AxSpA poses a considerable financial burden to patients, caregivers, society, and the National Health Service (NHS). A recent (2022) economic model commissioned by the National Axial Spondyloarthritis Society (NASS) reported that delays to axSpA diagnosis (averaging 8.5 years) costs the UK economy an estimated £18.7 billion each year, which is mainly attributed to time off work, out-of-pocket medical expenses, non-prescription (over the counter) drugs, travel costs and paid-for exercise (31).

Treatments for axSpA aim to control symptoms and delay disease progression by reducing damage to the joints and spine (32) (Section B.1.3.4).

- Initial pharmacological treatment for axSpA includes non-steroidal anti-inflammatory drugs (NSAID). For patients with an inadequate response, intolerance, or contraindication to NSAIDs, first-line treatment are tumour necrosis factor-alpha (TNF-α) inhibitors, followed by second-line biological disease-modifying anti-rheumatic drugs (bDMARD; TNF-α or interleukin [IL]-17A inhibitors), or targeted synthetic DMARDs (tsDMARD), such as Janus

kinase [JAK] inhibitors) (33, 34).

- Treatment choice for second-line (post TNF-α inhibitor failure) and later therapy is guided by patient preference, symptoms, and comorbidities (34, 35).

Despite currently available treatments, there is an unmet need for therapies with a rapid, effective, and sustained response that improve patient QoL (29, 36-43) (Section B.1.3.5).

- While TNF-α inhibitors are considered standard-of-care, clinical trial and real world evidence (RWE) data report that 50–70% of patients with axSpA do not achieve a 40% improvement in their disease symptoms with first-line TNF-α inhibitors (defined as Assessment of SpondyloArthritis international Society 40% response [ASAS40] after 24 weeks) (36-40).
- A longitudinal study from Spain also reported that although 76.8% of patients who receive a bDMARD achieve remission or low disease activity (defined as Ankylosing Spondylitis Disease Activity Score [ASDAS] <1.3 or ASDAS <2.1, respectively), only 40% of patients maintain this response up to 2 years (44).
- Notably, treatment switching after first-line TNF-α inhibitor failure is associated with a lower clinical response to a second-line TNF-α or IL-17A inhibitor (36, 41). Treatment failure is also associated with reduced quality of life (QoL) outcomes, risk of progression, and further functional impairment (42, 43).
- Although currently available biologic therapies reduce disease activity, the impact on fatigue is limited, with 80% of patients continuing to experience severe fatigue (29).

Bimekizumab is the only approved humanised immunoglobulin monoclonal antibody that binds to IL-17F in addition to IL-17A, pivotal drivers of inflammation, in order to inhibit the IL-17 pathway (45, 46) (Section B.1.3.4.3).

- Bimekizumab is the first biologic designed to selectively inhibit both IL-17A and IL-17F, cytokines with overlapping biology that are independent pivotal drivers of inflammation in axSpA. Hence, the inhibition of IL-17F in addition to IL-17A may lead to greater resolution of inflammation than inhibition of IL-17A alone (45-51)
- Bimekizumab is anticipated to be used in clinical practice for the treatment of:
    - Adults with active nr-axSpA with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately or are intolerant to NSAIDs, and
    - Adults with active AS who have responded inadequately or are intolerant to conventional therapy (NSAIDs and physiotherapy) (Appendix C) (52).
- Therefore, bimekizumab is expected to be positioned first-line (after NSAID failure) in patients who are contraindicated to TNF-α inhibitors, and second-line and later for all other patients with axSpA.

B.1.1 Decision problem

B.1.1.1 Comparators

According to National Institute for Health and Care Excellence (NICE) guidance, if a health technology is likely to provide similar or increased health benefits at similar or lower costs compared to health technologies previously recommended in the same indication then a cost comparison can be conducted (53).

The NICE cost-comparison route is proposed for the appraisal of bimekizumab. This submission focuses on part of the technology's marketing authorisation, in line with the recommended population for the proposed comparator ixekizumab in TA718 (54). Ixekizumab is recommended by NICE as an option for treating active ankylosing spondylitis (AS) that is not controlled well enough with conventional therapy, or active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation (shown by elevated C-reactive protein [CRP] or magnetic resonance imaging [MRI]) that is not controlled well enough with non-steroidal anti-inflammatory drugs (NSAID), in adults. It is recommended only if tumour necrosis factor (TNF)-alpha inhibitors are contraindicated or otherwise not suitable after primary non-response to a TNF-α inhibitor or after a poor response or loss of response to TNF-α inhibitors.

In addition, advisory board clinicians (35) and evidence from previous health technology assessments (HTA) (55, 56) suggest that the interleukin (IL)-17A inhibitors, ixekizumab and secukinumab, are the relevant comparators for this submission. IL-17A inhibitors have a similar mechanism of action to bimekizumab, which inhibits IL-17F in addition to IL-17A. Ixekizumab is the most similar treatment, in terms of efficacy and safety (Appendix D) and the most likely treatment to be displaced by bimekizumab in axSpA. Secukinumab trial evidence contains more heterogeneous dosing regimens and posologies. Secukinumab usage in the National Health Service (NHS) is similarly variable. There are two licenced doses in ankylosing spondylitis (AS), 150 mg and 300 mg delivered by subcutaneous (SC) injection once monthly (57). In non-radiographic axial spondyloarthritis (nr-axSpA), only the 150 mg monthly SC dose is licenced (57). However, there is substantial off-label secukinumab use in axSpA in the UK and US (35, 58-60), including both more frequent (more often than monthly) and higher (300 mg doses are used in nr-axSpA and AS, and not only in patients who have lost response after trying a 150 mg dose of secukinumab) doses. Common extra-articular and peripheral manifestations such as concomitant peripheral arthritis or plaque psoriasis, and higher patient weight (>90 kg), may change the recommended maintenance dose for secukinumab (57), while this is not true of ixekizumab. Market research appears to indicate that weight and age are correlates of use of the higher 300 mg dose (59). An indirect comparison with secukinumab's trial evidence is less likely

to be representative of its use in NHS practice than a similar comparison with ixekizumab's evidence. Therefore, ixekizumab is the most relevant comparator.

Full network meta-analysis (NMA) results including secukinumab are presented in B.3.9 and Appendix D, but the base case analyses do not contain the 300 mg secukinumab dose. While the 300 mg secukinumab dose is licenced in AS, only an intravenous (IV) induction regimen was identified in the systematic literature review (SLR) from the MEASURE 3 trial. This is not the licenced regimen, and so the 300 mg secukinumab dose was not included in the base case NMA (61). An NMA scenario analysis is presented in Section B.3.9 that allows secukinumab trials with IV induction at both 150 mg and 300 mg doses, MEASURE 1 and MEASURE 3, to be included in the network (61, 62). The cost-comparison analysis presented in Section B.4 includes bimekizumab, ixekizumab, and the 150 mg and 300 mg[a] secukinumab doses.

B.1.1.2 Population

Bimekizumab (Bimzelx®) is anticipated to be indicated for the treatment of adults with:

- Active nr-axSpA with objective signs of inflammation as indicated by elevated CRP and/or MRI who have responded inadequately or are intolerant NSAIDs (Appendix C)
- Active AS who have responded inadequately or are intolerant to conventional therapy (NSAIDs and physiotherapy) (Appendix C) (52).

The decision problem addressed in this submission is provided in Table 1, which outlines any differences from the NICE final scope (63).

[a] Note that secukinumab 300 mg is included as a comparator in both the AS and nr-axSpA populations, given that this dose is used in clinical practice in both populations. In market share data collected by Genactis, the 300 mg dose represents 25% of secukinumab use in nr-axSpA, and 34% of secukinumab use in AS (58). In market share data collected by Therapy Watch, the 300 mg dose represents 29.2% of secukinumab use across the nr-axSpA and AS populations (59).

Table 1: The decision problem

	Final scope issued by NICE (63)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with active axSpA	• Adults with active AS that is not controlled well enough with conventional therapy and where TNF-α inhibitors are not suitable or do not control the condition well enough. • Adults with active nr-axSpA with objective signs of inflammation (shown by elevated CRP or MRI) that is not controlled well enough with NSAIDs, and where TNF-α inhibitors are not suitable or do not control the condition well enough.	Aligns with the NICE recommendation for the IL-17A inhibitor, ixekizumab, and thus with the current positioning of the comparator treatment.
Intervention	Bimekizumab (Bimzelx®)	Bimekizumab (Bimzelx®)	–

Comparator(s)	**For active nr-axSpA:**
	• TNF-α inhibitors:
	  ○ Adalimumab
	  ○ Certolizumab pegol
	  ○ Etanercept
	  ○ Golimumab
	• IL-17A inhibitors:
	  ○ Secukinumab
	  ○ Ixekizumab
	• JAK inhibitors
	  ○ Upadacitinib
	• Established clinical management without biological treatments
	For active AS:
	• TNF-α inhibitors:
	  ○ Adalimumab
	  ○ Certolizumab pegol
		Ixekizumab (IL-17A inhibitor), secukinumab (IL-17A inhibitor)	Ixekizumab is the most relevant comparator:
			• Bimekizumab and ixekizumab display equivalent affinity for IL-17A in vitro (46)
			• Ixekizumab is the most similar treatment, in terms of efficacy, (NMA; Section B.3.9 and Appendix D). Bimekizumab is therefore expected to provide similar health benefits vs ixekizumab at a lower cost (Section B.3.12).
			• Both ixekizumab and bimekizumab are subcutaneously delivered Q4W. Ixekizumab has a single additional induction dose compared to no induction doses with bimekizumab.
			• Ixekizumab is the most likely treatment to be displaced by bimekizumab in axSpA. Market research data on dynamic patient share (new patient starts) estimate that ixekizumab has a 7% share of the UK market, with an 18% share in patients who have had inadequate response to first-line biologic. When estimating the TNF-α

	Final scope issued by NICE (63)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	○ Etanercept ○ Golimumab ○ Infliximab • IL-17A inhibitors: ○ Secukinumab ○ Ixekizumab • JAK inhibitors ○ Upadacitinib ○ Tofacitinib (subject to NICE evaluation • Established clinical management without biological treatments		contraindicated population market shares by removing TNF-α inhibitors and recalculating, ixekizumab has a 25% share of the contra-indicated market (64). Secukinumab is included in the comparison but was not considered to be the most relevant comparator for several reasons: • Secukinumab axSpA trials contain numerous doses and posologies, which complicates comparisons of efficacy • Secukinumab's in vitro IL-17A affinity is approximately 50–100 times lower than ixekizumab's and bimekizumab's (65). • There is substantial off-label secukinumab use tending toward greater dose intensity (35, 58-60) • Within license use of secukinumab results in higher doses in the presence of common extra-articular and peripheral manifestations such as concomitant peripheral arthritis, plaque psoriasis, and higher patient weight (>90kg). These manifestations and comorbidities may increase the recommended dose for secukinumab dependant on indication (57). Weight and age appear to correlate with use of the higher 300 mg dose (59). Note that secukinumab 300 mg is included as a comparator in both the AS and nr-axSpA populations, given that this dose is used in UK clinical practice in both populations (35). In market share data collected by Genactis, the 300 mg dose represents 25% of secukinumab use in nr-axSpA, and 34% of secukinumab use in AS (58). In market share data collected by Therapy Watch, the 300 mg dose represents 29.2% of

	Final scope issued by NICE (63)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			secukinumab use across the nr-axSpA and AS populations (59).
Outcomes	**The outcome measures to be considered include:** • Disease activity • Functional capacity • Disease progression • Pain • Peripheral symptoms (including enthesitis, peripheral arthritis, and dactylitis) • Symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease, and psoriasis) • Adverse effects of treatment • HRQoL	• Composite outcome (ASAS40) • Disease activity (ASDAS, BASDAI) • Functional capacity (BASFI) • MRI Inflammation of SIJ (SPARCC) • Nocturnal spinal Pain (NSP) • Peripheral manifestations, including enthesitis • Adverse effects of treatment, including incidence of uveitis • HRQoL (ASQoL, SF-36 PCS)	The incidence of dactylitis in axSpA is estimated to be 6% and therefore is not a core manifestation (66)
Subgroups to be considered	AS • b/tsDMARD naïve • b/tsDMARD experienced nr-axSpA • b/tsDMARD naïve • b/tsDMARD experienced	AS • b/tsDMARD naïve • b/tsDMARD experienced nr-axSpA • b/tsDMARD naïve • b/tsDMARD experienced	–

Abbreviations: AS, ankylosing spondylitis; ASA40, Assessment of SpondyloArthritis International Society 40% response; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; axSpA; b/tsDMARD, biological/targeted synthetic disease modifying anti-rheumatic drug; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; HRQoL, health related quality of life; IL, interleukin; JAK, Janus kinase; MRI, magnetic resonance; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, nonsteroidal anti-inflammatory drug; NSP, nocturnal spine pain; PCS, psychical component summary; Q4W, every 4 weeks' SF-36, Short-Form 36; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of Canada; TNF-α, tumour necrosis factor alpha; UK, United Kingdom.

B.1.2 Description of the technology being appraised

Table 2 summarises the technology (bimekizumab) being appraised in this submission. The (draft) summary of product characteristics (SmPC) and the United Kingdom (UK) public assessment report are presented 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, cytokines with overlapping biology that are independent pivotal drivers of inflammation in axSpA. Hence, the inhibition of IL-17F in addition to IL-17A may lead to greater resolution of inflammation than inhibition of IL-17A alone (45-51)
Marketing authorisation/CE mark status	Bimekizumab does not yet have marketing authorisation for the indication in this submission. • EMA: submission made 08/2022, with CHMP positive opinion received 04/2023 (67) • MHRA: submission made 05/2023
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Bimekizumab is currently indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy (68). The anticipated indication update is for axSpA, with or without radiographic damage: • Adults with active nr-axSpA with objective signs of inflammation as indicated by elevated CRP and/or MRI who have responded inadequately or are intolerant NSAIDs, and • Adults with active AS who have responded inadequately or are intolerant to conventional therapy (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 axSpA is 160 mg (given as one SC injection) Q4W. Consideration should be given to discontinuing treatment in patients who have shown no improvement by 16 weeks of treatment.
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment	**Acquisition cost (two pens or syringes pre-filled with 160 mg/mL)** • List price: £2,443 • PAS price: [redacted] **Annual cost of treatment** • List price: £15,934.03 • PAS price: [redacted]
Patient access scheme (if applicable)	Bimekizumab is available at a cost of [redacted] per 160 mg/mL solution for injection in pre-filled pen or syringe, via a confidential simple discount patient access scheme.

Abbreviations: AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; CHMP, Committee for Medicinal Products for Human Use; CRP, C-reactive protein; IL, interleukin; MHRA, Medicines and Healthcare products Regulatory Agency; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, non-steroidal anti-inflammatory drug; Q4W, every 4 weeks; SC, subcutaneous; UK, United Kingdom.

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

B.1.3.1 Disease overview

Spondyloarthritis refers to a group of interrelated chronic rheumatic inflammatory diseases (69, 70). Based on the main clinical manifestation, spondyloarthritis is classified into two major subtypes: axial or peripheral (71). AxSpA is generally characterised by inflammation affecting the axial skeleton (including the spine and sacroiliac joints [SIJ] of the pelvis) (1, 2, 72), whereas peripheral spondyloarthritis primarily affects the peripheral joints. Both conditions can also affect various extra-articular structures (e.g. the gut, skin, eye, and aortic valve) (70).[b]

There are two subtypes of axSpA: nr-axSpA and AS (also called radiographic axSpA [r-axSpA]) (1-3). If there is radiographic evidence of structural damage to SIJs according to the modified New York (mNY) radiographic criterion, the disease is classified as AS (3), while in nr-axSpA there is no definitive radiographic evidence of such structural damage to the SIJ, but there are other objective signs of inflammation on MRI or presence of elevated CRP (1, 3, 73). However, it should be noted that the NICE appraisal for ixekizumab (TA718) and the Assessment of Spondyloarthritis International Society European League Against Rheumatism (ASAS-EULAR) recommendations refer to axSpA as a single disease spectrum (34, 54). This is supported by clinicians at UK advisory boards organised by UCB (N=9) (35), who indicated that many patient diagnoses and treatment decisions are not differentiated by radiographic status (35). Furthermore, multiple studies[c] report that patients with nr-axSpA and AS are generally similar with respect to clinical presentation and disease burden (38, 74, 75) (Section B.1.3.3). Thus, whilst this submission presents clinical evidence for both subtypes in separate Phase 3 trials (Section B.3), there is often little distinction between nr-axSpA and AS in clinical practice.

AxSpA is an immune-mediated inflammatory disease, with proinflammatory cytokines being major disease mediators (76). IL-17A and IL-17F have been shown to be key drivers of inflammation and new bone formation in axSpA. Dual blockade of IL-17F in addition to IL-17A has been shown to result in a greater resolution of inflammation and inhibition of pathological bone formation when compared with IL-17A inhibition alone in in vitro pre-clinical studies (49). Innate immune cells producing IL-17A & F (e.g. mucosal associated invariant T [MAIT] cells, γδ T cells), independent of IL-23, play an important role in axSpA disease pathogenesis (77-79), and

[b] Peripheral spondyloarthritis includes conditions such as reactive arthritis, psoriatic arthritis, enteropathic spondyloarthritis, and undifferentiated spondyloarthritis (12).

[c] Randomised controlled trials [RCT], cohort studies, and systematic literature reviews [SLRs]).

elevated IL-17A and IL-17F levels are associated with chronic inflammation alongside some other proinflammatory cytokines (80). IL-17 (including IL-17A and IL-17F) is also involved in the pathogenesis of several other diseases, including psoriatic arthritis (PsA), and psoriasis (PSO), which have overlapping clinical features (81, 82).

B.1.3.2 Epidemiology

There are limited data on the epidemiology of axSpA overall, with most data coming from populations with AS only (83-85); resulting in a relative paucity of literature encompassing the non-radiographic stage.

Overall, axSpA is estimated to affect 1 in 200 (0.5%) patients in the UK (8). Only one study provides prevalence estimates for nr-axSpA, reporting an nr-axSpA prevalence of 0.35%, and an equivalent AS prevalence of 0.35% in the US (12). However, it is believed that these figures could underestimate the true prevalence of axSpA, due to an average delay in diagnosis of 8.5 years (7, 8), in part due to imaging uncertainty and initial misdiagnosis, particularly in women (31, 85), with the burden of delays being significantly longer in females than males (9, 10). Notably, AS is more prevalent in males (59–77% male), whereas nr-axSpA is more prevalent in females (52–68% female) (5, 73, 86).

B.1.3.3 Disease burden

AxSpA is a heterogenous disease in which various clinical features and manifestations result in a burdensome clinical profile (17, 18, 20, 21, 87), encompassing axial symptoms (such as chronic back pain) (Section B.1.3.3.1.1), peripheral manifestations (Section B.1.3.3.1.2), and extra-articular manifestations (Section B.1.3.3.1.3), along with comorbidities (Section B.1.3.3.1.4) (88). Clinical features result in a high humanistic burden (Section B.1.3.3.4), with nr-axSpA and AS associated with a similar burden on physical function, mood disturbance, work productivity, and quality of life (QoL) (28) and similar degrees of anxiety and depression (27).

B.1.3.3.1 *Clinical burden*

The overarching clinical opinion is that axSpA represents one disease spectrum encompassing non-radiographic (nr-axSpA) and radiographic (AS) stages. Some patients with nr-axSpA develop irreversible radiographic changes on the SIJs over time and therefore progress to AS, although many nr-axSpA will never progress to that stage (34, 35, 88). Aside from the presence or absence of radiographic structural damage, the frequency and severity of symptoms and disease burden experienced by patients with nr-axSpA and AS are the same (1, 29, 89, 90). Furthermore, UK clinicians (N=9) consulted by UCB in three advisory boards asserted that treatment decisions are not differentiated by radiographic status (35).

B.1.3.3.1.1 Axial symptoms

The main axial symptoms of axSpA are chronic (≥3 months) back pain and stiffness, which affect mobility and the ability to perform activities of daily living (17, 18). The median age of axial symptoms onset is estimated to be 26 years (interquartile range [IQR] 20–34 years) (91), and the average age at onset of chronic back pain is similar for both AS (28 years) and nr-axSpA (27 years) (4). Notably, a Swedish population study recently reported no significant differences in any pain measure (number of pain regions, pain groups, pain intensity, frequency of unacceptable pain, or pain sensitivity) between patients with nr-axSpA and AS (92, 93).

B.1.3.3.1.2 Peripheral manifestations

Many patients with axSpA also experience peripheral manifestations, the most common of which are arthritis (affecting an estimated 28–57% of patients), enthesitis (affecting an estimated 37–74% of patients), and dactylitis (affecting an estimated 6% of patients) (1, 19, 30). An SLR and meta-analysis reported that patients with nr-axSpA and AS share a similar clinical presentation (74). Patients with nr-axSpA report slightly higher prevalence of peripheral manifestations than patients with AS, including PsA (35.2% vs 32.8%, respectively), dactylitis (7.6% vs 5.6%, respectively) and any enthesitis (30.1% vs 23.0%, respectively) (74).

B.1.3.3.1.3 Extra-articular manifestations

Anterior uveitis is the most common extra-articular manifestation, affecting 16–40% of patients with axSpA (94-96). Other commonly reported extra-articular manifestations include PSO (10–27%) and inflammatory bowel disease (IBD) (5–10%) (94, 97, 98).

B.1.3.3.1.4 Comorbidities

Patients with axSpA have an increased risk for several comorbid conditions, the most common of which are hypertension (22.3%), any infection (18.3%), hyperlipidaemia (17.1%), obesity (13.5%) and any cardiovascular disease (CVD, 12.3%). These comorbidities are associated with higher axSpA disease severity, lower work productivity, and increased mortality rates, and thus represent a significant clinical burden in addition to the manifestations of axSpA (99).

B.1.3.3.2 *Disease progression*

An estimated 60% of patients with nr-axSpA progress to AS during the lifelong course of their disease, with an approximate rate of 1% per year (5, 6, 11). Further progression of AS may lead to irreversible new bone formation between the vertebrae, which is a major determinant for long-term disability (100-102).

B.1.3.3.3 *Mortality*

There are limited data on the impact of axSpA on mortality. In a retrospective UK database analysis, all-cause mortality was higher among patients with axSpA compared with the general population (hazard ratio [HR]: 1.531; 95% confidence interval [CI]: 1.291, 1.816; p<0.001) (103). The most common causes of death in the axSpA cohort were coronary heart disease, cerebrovascular disease, and malignant neoplasm of the bronchus and lung (103).

B.1.3.3.4 *Humanistic burden*

Patients experience a considerable disease burden that impacts their capacity to carry out activities of daily living and negatively impacts their QoL (16, 23, 24, 104-106). Although most research on the health-related quality of life (HRQoL) burden in axSpA focuses on AS. In alignment with the similar burden of disease symptoms and functional impact across nr-axSpA and AS, this detrimental impact on patient HRQoL is generally considered comparable between nr-axSpA and AS (73, 90, 107). As axSpA is a long-term, progressive disease with a median age of onset of 26 years, the QoL burden is lifelong (8).

The key symptoms of axSpA are chronic back pain, morning stiffness, and fatigue (93), with chronic back pain experienced by almost all (97.5–100%) patients during the course of their disease (89). As such, patients with axSpA are often chronic users of pain medications (108). Compared with other rheumatic diseases, mean overall and joint pain scores are significantly higher in patients with axSpA, and comparable with pain scores in patients with PsA (109).

Fatigue is a recognised symptom in both nr-axSpA and AS, and is a component of the widely used index for axSpA disease activity (BASDAI) (29, 109, 110). Fatigue has a substantial impact on patient QoL and leads to limitations in daily life (such as physical and social functioning) and reduced global wellbeing and health, with severe fatigue leading to a greater burden than low fatigue (29, 89, 110, 111).

Treatment control of axSpA is also associated with improved HRQoL(29, 112). Disease activity scores (including BASDAI and Ankylosing Spondylitis Disease Activity Score [ASDAS]-CRP) significantly correlate with both anxiety and depression in patients with AS, and evidence demonstrates that treatment is associated with significant improvements in all aspects of HRQoL, from disease activity, pain and physical functioning to work stability, patients' psychological health and global QoL (113).

The clinical symptoms and delayed diagnosis can result in psychological consequences, including distress, depression, anxiety, and suicidal thoughts (26, 27, 31, 114). Both nr-axSpA

and AS have similar degrees of anxiety and depression (27), and are associated with lower physical function, mood disturbance, work productivity, QoL, and disability (28).

B.1.3.3.5 *Economic burden*

There is a lack of data regarding the economic burden of axSpA. However, it is estimated that 95% of axSpA cases are diagnosed under the age of 45 years (34), and approximately 40% of working-age patients with axSpA in the UK are unemployed or have retired early (54). Work impairment is linked to disease severity (115), with higher disease severity associated with up to four times the indirect cost burden compared with lower disease activity (116). Lost work due to axSpA represents a substantial economic burden, with the costs of early retirement, absenteeism, and presenteeism due to AS estimated to be £8,100, £411, and £3,425 per patient per year, respectively (106). Indeed, an SLR of 10 studies across Europe reported that indirect costs account for 53.4%–62% of the total costs associated with AS (116).

In a retrospective study conducted in the United States (US), mean annual direct costs were shown to be three-fold higher in those with AS than in matched control patients (mean [standard deviation [SD]]: $33,285 [$46,363] vs $8,310 [$32,260]), with increased use of outpatient services and outpatient pharmacy costs found to be the key drivers of this difference in total direct costs (117).

Notably, a recent (October 2022) economic model commissioned by the National Axial Spondyloarthritis Society (NASS) reported that delays in the diagnosis of axSpA (an average of 8.5 years) costs the UK economy an estimated £18.7 billion each year, with costs mainly attributed to time off work, out-of-pocket medical expenses, non-prescription (over the counter) drugs, travel costs and paid-for exercise. The authors estimate that reducing the diagnosis delay by one year would save the UK economy approximately £167,000 per patient in health care costs, out of pocket costs, and productivity losses (31).

B.1.3.4 Clinical pathway of care

B.1.3.4.1 *Diagnosis*

A diagnosis of AS is often based on the radiographic evidence of sacroiliitis according to the radiographic criterion of the mNY classification criteria (118, 119). Nr-axSpA can be challenging to diagnose, as patients experience axSpA symptoms without structural changes on x-rays or MRI inflammation (84, 88).

B.1.3.4.2 *Treatment pathway*

The treatment pathway for patients who have been diagnosed with axSpA as per guidelines and technology appraisals published by NICE is summarised in Figure 1. The guidance provided by the British Society of Rheumatology/ British Health Professionals in Rheumatology (BSR/BHPR) and ASAS/EULAR is broadly consistent with the treatment recommendations provided by NICE (32, 54, 76, 88, 120-125).

Treatments for axSpA aim to control the symptoms and delay the progression of axSpA by reducing damage to the joints and spine by suppressing inflammation (32). Current treatment includes a combination of physiotherapy and pharmacological approaches (32). The initial pharmacological treatments for axSpA are NSAIDs to control pain and stiffness, as well as maintain mobility and reduce inflammation (126). Treatment with NSAIDs alongside physiotherapy is referred to as 'conventional therapy' (32). In patients with axSpA with an inadequate response to or intolerance of NSAIDs, available therapies in England include: TNF-α, IL-17A, and Janus kinase (JAK) inhibitors (32, 54, 76, 122-125) (Figure 1). Treatment response to TNF-α inhibitors should be assessed after 12 weeks, and IL-17A and JAK inhibitors should be assessed after 16–20 weeks (32, 54, 76, 122-124). If the response is considered suboptimal[d] patients switch treatment, with clinicians preferring an alternative mechanism of action (32, 35, 54, 76, 122-124). However, the choice of second-line therapy is not well defined, and is guided by patient preference, symptoms, and comorbidities (34, 35, 88).

The ASAS-EULAR guidelines state that the primary goal of treating patients with axSpA is to maximise long-term HRQoL through (34):

- Control of symptoms and inflammation
- Prevention of progressive structural damage
- Preservation/normalisation of function and social participation.

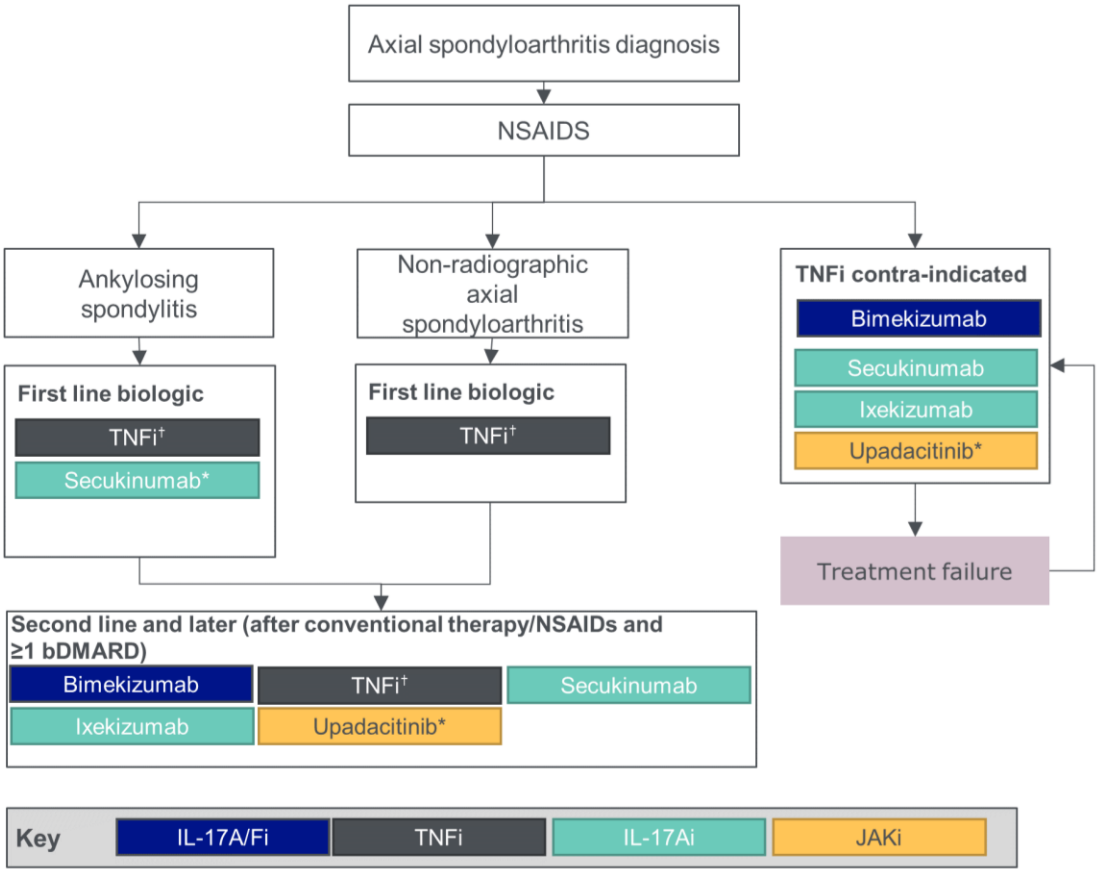
Biologic/targeted synthetic disease modifying anti-rheumatic drugs (b/tsDMARD) directly target the signalling pathways involved in axSpA pathogenesis, thereby reducing disease progression (127).

[d] Treatment should only be continued if there is clear evidence of response, defined as: a reduction in the BASDAI score to 50% of the pre-treatment value or by 2 or more units and a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

- TNF-α inhibitors (adalimumab, etanercept, certolizumab pegol, golimumab, infliximab) target TNF-α to inhibit the downstream signalling pathways associated with inflammation and bone formation for the treatment of AS (128).
- IL-17A inhibitors (secukinumab, ixekizumab) target the proinflammatory IL-17 cytokine family, reducing the release of other proinflammatory cytokines, and potentially reducing the progression of radiographic damage (new bone formation) (129-131)
- JAK inhibitors (upadacitinib) target the JAK cytokine family (specifically JAK1), inhibiting various pro-inflammatory cytokines such as IL-7 and IL-21 (132).

In nr-axSpA, bimekizumab is expected to be indicated in patients who have responded inadequately or are intolerant to NSAIDs, while in AS, bimekizumab is expected to be indicated in patients who have responded inadequately or are intolerant to conventional therapy (NSAIDs and physiotherapy) (Appendix C) (52). The most relevant comparator for this submission is the IL-17A inhibitor, ixekizumab (see Table 1 and Section B.1.1 for justification).

Figure 1: NICE treatment pathway for axSpA including proposed position of bimekizumab



†Includes adalimumab, etanercept, certolizumab pegol, golimumab, infliximab*
*Only in ankylosing spondylitis

Abbreviations: bDMARD, biologic disease modifying antirheumatic drug; IL-17Ai, interleukin 17A inhibitor; JAKi, Janus kinase inhibitor; NICE, National Institute for Health and Care Excellence; NSAIDS, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitor.

B.1.3.4.3 *Bimekizumab*

Bimekizumab is the first biologic designed to selectively inhibit both IL-17A and IL-17F, cytokines with overlapping biology that are independent pivotal drivers of inflammation in axSpA. Hence, the inhibition of IL-17F in addition to IL-17A may lead to greater resolution of inflammation than inhibition of IL-17A alone (45-51) (Appendix C).

B.1.3.5 Unmet need

AxSpA is an underdiagnosed, progressive disease that requires lifelong treatment to control the symptoms and delay progression (32). Patients have a broad spectrum of symptoms, with chronic back pain, morning stiffness and fatigue the main symptoms experienced (17, 18), and many patients presenting with peripheral manifestations (e.g. arthritis), extra-articular manifestations (e.g. uveitis and PSO), and comorbidities (e.g. heart disease) (19). These symptoms are associated with a humanistic burden, including severe fatigue, anxiety, and depression (26, 27, 31, 114). The symptom profile leads to limited mobility, functional impairment, and a decreased QoL (133). Notably, if disease progresses it can lead to irreversible spinal deformities (97), hence early intervention and achievement of meaningful clinical responses are pivotal to minimising the clinical impact of disease.

ASAS-EULAR guidelines recommend setting treatment targets between patient and clinician with ASDAS low disease activity or remission as viable targets (34). Higher treatment targets such as ASDAS low disease activity correlate with greater improvements in HRQoL outcomes as well as lower spinal progression and better work productivity (34, 43, 134). However, real world evidence has shown that the majority of patients treated with a biologic do not achieve or maintain higher treatment targets such as low disease activity longer term (42). Therefore, there is a need for new treatments that can provide the opportunity to elevate treatment targets in order to prevent longer term structural damage and disability.

Following diagnosis, patients typically receive conventional treatment; however, ≥40% of patients progress to bDMARDs after 4 weeks of NSAIDs (135). Whilst currently available bDMARDs improve disease outcomes, clinical trial data show that 50–65% of patients with axSpA do not achieve a clinically meaningful response[e] after receiving a first-line TNF-α inhibitor for 24 weeks (36), and 58– 64% of patients receiving IL-17A inhibitors do not achieve a clinically meaningful response after 16 weeks of treatment (after first- or second line treatment) (36-38). A longitudinal study from Spain also reports suboptimal long-term efficacy with available bDMARDs (TNF-α or

[e] Defined as Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50)

IL-17A inhibitors), with only 40% of patients maintaining remission or low disease activity[f] over three consecutive visits (up to 2 years' follow-up) (44). Notably, treatment switching after first-line TNF-α inhibitor failure is associated with a lower clinical response to a second-line TNF-α or IL-17A inhibitor (36, 41). Patients who experience TNF-α inhibitor failure also experience worse physical function, HRQoL and work productivity (41).

Subsequent to TNF-α inhibitor failure, there are few safe and effective treatment options with distinct modes of action. Patients typically receive secukinumab or ixekizumab, both of which inhibit IL-17A alone (34, 35, 54, 76, 123). There is a need for therapies with different mechanisms of action to enable greater treatment choices for patients who respond inadequately to earlier therapy lines. This is especially true for patients who cannot tolerate adverse effects associated with TNF-α inhibitors or for whom TNF-α inhibitors are contraindicated (136). Prevailing preference of UK clinicians consulted as part of three UCB advisory boards (N=9) was to try a different mechanism of action if patients do not respond to a TNF-α inhibitor after 12 weeks of therapy (primary failure) (35). Clinicians consulted in an August 2022 advisory board considered the lack of sustained effective treatment options for adults with axSpA after TNF-α inhibitor failure to be the most important unmet need in axSpA (35).

Unlike IL-17A-specific inhibitors, bimekizumab enables neutralisation of IL-17A/A, IL-17A/F and IL-17F/F (45, 46, 49, 51, 137). Elevated IL-17A and IL-17F levels drive inflammation and new bone formation in axSpA, and bimekizumab is the only selective inhibitor of IL-17F in addition to IL-17A. In in vitro models, bimekizumab selectively and potently suppresses the expression of inflammation-related genes, production of inflammatory cytokines, and immune cell migration more effectively than inhibition of IL-17A alone (138). Bimekizumab therefore offers patients with axSpA a new treatment option with a novel mechanism of action, and it is anticipated that bimekizumab with its dual inhibition of IL-17F and IL-17A will lead to a more complete inhibition of inflammation than the inhibition of IL-17A alone with ixekizumab and secukinumab.

There is a clear need for novel treatments that achieve and maintain clinically meaningful treatment targets in axSpA, regardless of prior bDMARD exposure as many patients with suboptimal treatment response will have previously failed on the currently available bDMARDs. New treatments with novel mechanisms of action are therefore needed to provide clinicians with greater treatment choices, reduce the clinical burden, and prevent irreversible structural damage.

[f] Defined as ASDAS <1.3 or ASDAS <2.1, respectively

B.1.4 Equality considerations

In 2021, a policy paper published by the Department of Health and Social Care highlighted the need to improve women's health outcomes (139). Nr-axSpA is more prevalent in females than males (52–68% female) (5, 73, 86), and females typically have a worse response to TNF-α inhibitors than males (9).

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

Seven previous National Institute for Health and Care Excellence (NICE) technology appraisals (TAs) have been published for treatments in ankylosing spondylitis (AS) and/or non-radiographic axial spondyloarthritis (nr-axSpA): TA383 (122), TA407 (123), TA497 (124), TA718 (54), TA719 (76), TA829 (32), and TA861 (56).

- The key clinical outcomes used in the cost-effectiveness analyses in these appraisals were Bath Ankylosing Spondylitis Disease Activity Index 50% response (BASDAI50), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) change from baseline (CfB), Bath Ankylosing Spondylitis Functional Index (BASFI) CfB, and long-term change in BASFI over time (Section B.2.1).
  - Assessment of SpondyloArthritis international Society 20% response (ASAS20) and Assessment of SpondyloArthritis international Society 40% response (ASAS40) were also considered by two companies in TA383 (122).
  - Additional outcomes used in the assessment of clinical effectiveness in previous appraisals were Bath Ankylosing Spondylitis Metrology Index (BASMI), ASAS partial remission, total back pain score, and Ankylosing Spondylitis Quality of Life (ASQoL).
- The cost types considered in previous NICE appraisals were drug acquisition, administration, monitoring, disease management and adverse event costs (Section B.2.2).

NICE has published guidance following seven technology appraisals for treatments in nr-axSpA and/or AS (summarised in Table 3). The comparators for bimekizumab in the current cost-comparison analysis are the IL-17A inhibitors, ixekizumab and secukinumab (Section B.1.1).

Table 3: Summary of NICE technology appraisals in nr-axSpA and/or AS

Technology	Appraisal	Date published	Appraisal type	Indication	
				nr-axSpA	AS
TNF-α inhibitors†	TA383 (122)	September 2015	MTA	✓	✓
Secukinumab	TA407 (123)	August 2016	STA	–	✓
Golimumab	TA497 (124)	November 2017	FTA CC	✓	–
Ixekizumab	TA718 (54)	June 2021	STA	✓	✓
Secukinumab	TA719 (76)	June 2021	STA	✓	–
Upadacitinib	TA829 (32)	August 2022	FTA CC	–	✓
Upadacitinib	TA861 (56)	February 2023	STA CC	✓	–

†TNF-α inhibitors considered in TA383 included adalimumab, certolizumab pegol, etanercept, golimumab (AS only) and infliximab (AS only).
Abbreviations: AS, ankylosing spondylitis; CC, cost comparison; FTA, fast track appraisal; MTA, multiple technology appraisal; NICE, National Institute for Health and Care Excellence; nr-axSpA, non-radiographic axial spondyloarthritis; STA, single technology appraisal; TA, technology appraisal; TNF-α, tumour necrosis factor alpha.

B.2.1 Clinical outcomes and measures

Of the identified appraisals, four considered cost-effectiveness analyses. The clinical efficacy outcomes used in the cost-effectiveness analyses that were modelled to differ between technologies were:

- Assessment of SpondyloArthritis international Society 20% response (ASAS20)
- ASAS40
- Bath Ankylosing Spondylitis Disease Activity Index 50% response (BASDAI50)
- BASDAI change from baseline (CfB)
- Bath Ankylosing Spondylitis Functional Index (BASFI) CfB
- Long-term change in BASFI over time[g].

Additional outcome measures used in the assessment of clinical effectiveness in the identified appraisals were:

- Bath Ankylosing Spondylitis Metrology Index (BASMI)
- ASAS partial remission (ASAS PR)
- Total back pain score
- Ankylosing Spondylitis Quality of Life (ASQoL).

A summary of the clinical outcome measures used in previous appraisals and the committees' preferred assumptions is presented in Table 4[h].

All previously considered clinical outcomes are included in the NMA for the current submission (Section B.3.9 and Appendix D), with the exception of long-term change in BASFI over time and total back pain score. Long-term change in BASFI over time cannot be considered in the NMA due to a lack of long-term data in the included trials. Total back pain score is not included as an independent measure but is a component of other included measures.

[g] Note that long-term change in BASDAI over time was not modelled in previous appraisals; BASDAI was assumed to remain constant over time.
[h] Only clinical outcome measures referenced in the Final Appraisal Document for the relevant technology appraisal have been included.

Table 4: Summary of clinical outcome measures used in previous NICE appraisals

Technology	Appraisal	Indication	Clinical outcome measure	Included in cost-effectiveness model	Committee comments
TNF-α inhibitors	TA383 (122)	AS and nr-axSpA	ASAS20	Yes	• The committee considered that all TNF-α inhibitors showed a benefit compared with placebo in both conditions, based on the clinical outcome measures presented • The committee preferred to use the Assessment Group model, which separated the model into three key stages: the probability of initial response, the size of initial response for 'responders' and 'non-responders,' and the long-term trajectory of BASDAI and BASFI scores • The committee agreed with the Assessment Group's assumption that BASFI continues deteriorating during TNF-α inhibitor treatment, but at a slower rate compared with the natural history of disease; however, the committee disagreed with the assumption that a TNF-α inhibitor's effect on progression is delayed until Year 4 • The committee noted that the Assessment Group was unable to use the 2-point BASDAI change in the definition of response in the model due to a lack of data; however, in clinical practice response should be defined based on BASDAI 50, or a reduction of ≥2 units in BASDAI, together with a reduction in the spinal pain VAS by ≥2 cm
			ASAS40	Yes	
			BASDAI50	Yes	
			BASDAI CfB	Yes	
			BASFI CfB	Yes	
			Long-term change in BASFI over time	Yes	
			BASMI	No	
Secukinumab	TA407 (123)	AS	BASDAI50	Yes	• The committee concluded that secukinumab had similar efficacy to the TNF-α inhibitors, based on the clinical outcome measures presented • The committee concluded that for the purposes of the appraisal, the broad principles of the York model (TA383) (122) were appropriate
			BASDAI CfB	Yes	
			BASFI CfB	Yes	
			Long-term change in BASFI over time	Yes	
			ASAS20	No	
Golimumab	TA497 (124)	nr-axSpA	ASAS20	Not applicable[†]	• The committee considered that golimumab is clinically effective compared with placebo, and has similar clinical effectiveness to adalimumab, etanercept and
			ASAS40		
			BASDAI50		

Technology	Appraisal	Indication	Clinical outcome measure	Included in cost-effectiveness model	Committee comments
			ASAS PR		certolizumab pegol, based on the clinical outcome measures presented
			BASMI		
Ixekizumab	TA718 (54)	AS and nr-axSpA	BASDAI50	Yes	• The committee concluded that ixekizumab is effective compared with placebo, based on the clinical outcome measures presented • The committee considered that the structure of the model was appropriate
			BASDAI CfB	Yes	
			BASFI CfB	Yes	
			Long-term change in BASFI over time	Yes	
			ASAS40	No	
Secukinumab	TA719 (76)	nr-axSpA	BASDAI50	Yes	• The committee concluded that, compared with placebo, secukinumab increases the proportion of people having an ASAS40 response, BASDAI50 response and improved function as assessed by BASFI • The committee concluded that the structure of the company's model was appropriate for decision making
			BASDAI CfB	Yes	
			BASFI CfB	Yes	
			Long-term change in BASFI over time	Yes	
			ASAS40	No	
Upadacitinib	TA829 (32)	AS	ASAS40	Not applicable†	• The committee concluded that upadacitinib was more clinically effective than placebo, and that upadacitinib is likely to provide similar overall health benefits to secukinumab and ixekizumab, based on the clinical outcome measures presented
			BASDAI50		
			Total back pain score		
			ASQoL		
Upadacitinib	TA861 (56)	nr-axSpA	ASAS40	Not applicable†	• The committee concluded that the NMA was uncertain, but supported that upadacitinib has similar clinical effectiveness to secukinumab and ixekizumab, based on the clinical outcome measures presented
			BASDAI50		
			BASDAI CfB		
			BASFI CfB		

† Cost-comparison submission.
Abbreviations: AS, ankylosing spondylitis; ASAS; Assessment in Spondyloarthritis international Society; BASDAI; Bath Ankylosing Spondylitis Disease Activity Index; BASFI; Bath Ankylosing Spondylitis Functional Index; BASMI; Bath Ankylosing Spondylitis Metrology Index; BSR, British Society of Rheumatology; CfB; change from baseline; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis nr-axSpA, non-radiographic axial spondyloarthritis; TA, technology appraisal; TNF-α, tumour necrosis factor alpha.

B.2.2 Resource use assumptions

Resource use and associated costs considered in previous NICE appraisals in nr-axSpA and/or AS were:

- Drug acquisition costs
- Administration costs
- Monitoring costs
- Disease management costs
- Adverse event (AE) costs.

A summary of the costs used in previous appraisals and the committee's preferred assumptions is presented in Table 5.[i] No comments made by the committee on resource use or costing assumptions were considered relevant to the current appraisal.

Only drug acquisition costs are included in the current cost-comparison analysis for bimekizumab in axSpA. Administration costs are equivalent between bimekizumab, ixekizumab and secukinumab as all are administered SC; an initial training session with a nurse is required for each patient, after which all three treatments are self-administered at home. No additional monitoring requirements are anticipated for bimekizumab in addition to those required for ixekizumab or secukinumab. Disease management costs are assumed to be equivalent between bimekizumab, ixekizumab and secukinumab, given that the technologies are associated with similar efficacy[j]. As the safety profiles of bimekizumab, ixekizumab and secukinumab are similar (Section B.3.9.4 and Appendix D), AEs are not expected to be a key driver of incremental cost and are therefore not included in the analysis.

[i] Only resource use and costing assumptions referenced in the Final Appraisal Document for the relevant technology appraisal have been included.
[j] BASFI has been the basis for disease management cost equations used in previous appraisals (54, 76, 122); bimekizumab is associated with similar or improved BASFI compared with ixekizumab and secukinumab (Section B.3.9 and Appendix D).

Table 5: Summary of costs used in previous NICE appraisals

Technology	Appraisal	Indication	Included cost types	Committee comments
TNF-α inhibitors	TA383 (122)	AS and nr-axSpA	• Drug acquisition • Administration • Monitoring costs • Disease management • AE costs	• The committee considered that the modelled infusion cost for infliximab was too high, and the national tariff cost for delivering simple parenteral chemotherapy provided a better estimate • The committee concluded that vial sharing should not be considered for costing infliximab due to variation in sharing practices across the NHS • The committee noted that potential differences between the TNF-α inhibitors in their effects on EAMs may have cost implications, but there was insufficient evidence to incorporate this in the cost-effectiveness analysis
Secukinumab	TA407 (123)	AS	• Drug acquisition • Administration • Monitoring costs • Disease management • AE costs	• No comment was made by the committee on resource use or costing assumptions
Golimumab	TA497 (124)	AS	• Drug acquisition	• The committee considered that it was appropriate to assume that all resource use and costs other than drug acquisition costs are identical across golimumab and the comparators
Ixekizumab	TA718 (54)	AS and nr-axSpA	• Drug acquisition • Administration • Monitoring costs • Disease management • AE costs	• No comment was made by the committee on resource use or costing assumptions
Secukinumab	TA719 (76)	nr-axSpA	• Drug acquisition • Administration • Monitoring costs • Disease management • AE costs	• The committee considered that adalimumab biosimilar costs best represent the costs for first-line use of TNF-α inhibitors as a class
Upadacitinib	TA829 (32)	AS	• Drug acquisition • Administration • Monitoring	• The committee considered that it was uncertain whether upadacitinib would incur additional monitoring costs in the longer term
Upadacitinib	TA861 (56)	nr-axSpA	• Drug acquisition • Administration • Monitoring	• No comment was made by the committee on resource use or costing assumptions

Abbreviations: AE, adverse event; AS, ankylosing spondylitis; EAMS, extra-articular manifestations; ERG, Evidence Review Group; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; nr-axSpA, non-radiographic axial spondyloarthritis; TA, technology appraisal; TNF-α, tumour necrosis factor alpha.

B.3 Clinical effectiveness

The efficacy and safety of bimekizumab 160 mg every 4 weeks (Q4W) has been assessed in a clinical development programme including two Phase 3 randomised controlled trials (RCTs), with dual inhibition of interleukin (IL)-17A and IL-17F resulting in significant and rapid improvements in efficacy outcomes vs placebo (140-142) (Section B.3.1).

- BE MOBILE 1: adult patients with non-radiographic axSpA (nr-axSpA) who had either failed to respond to two different nonsteroidal anti-inflammatory drugs (NSAID) or had a history of intolerance or contraindication to NSAID therapy (140, 141).
- BE MOBILE 2: adult patients with ankylosing spondylitis (AS) who had either failed to respond to two different NSAIDs or had a history of intolerance or a contraindication to NSAID therapy (142, 143).

Both trials met their primary endpoints, with bimekizumab demonstrating a significant increase in Assessment of SpondyloArthritis International Society 40% (ASAS40) response across the disease spectrum at Week 16 vs placebo (47, 141, 142) (Section B.3.6.1).

- BE MOBILE 1: 47.7% vs 21.4%; odds ratio (OR): 3.51 (95% confidence interval [CI]: 2.0, 6.2); p<0.001, bimekizumab vs placebo, respectively
- BE MOBILE 2: 44.8% vs 22.5%; OR: 2.88 (95% CI: 1.71, 4.87); p<0.001, bimekizumab vs placebo, respectively

Across both trials, bimekizumab also demonstrated improvements vs placebo in secondary efficacy endpoints relating to disease activity, physical function, pain, and quality of life (QoL) at Week 16 (Section B.3.6.2.1).

- A higher proportion of patients achieved Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥1.3 to <2.1 (low disease activity [LDA])
  - BE MOBILE 1: 27.3% vs 14.7%) bimekizumab vs placebo, respectively
  - BE MOBILE 2: 28.4% vs 12.8%) bimekizumab vs placebo, respectively
- A higher proportion of patients achieved ASDAS major improvement (ASDAS-MI) (p<0.001 in both trials)
  - BE MOBILE 1: 27.3% vs 7.1%, OR: 19.0 (95% CI: 10.7,27.2) bimekizumab vs placebo, respectively
  - BE MOBILE 2: 25.8% vs 5.4%, OR: 18.6 (95% CI: 10.9, 26.3) bimekizumab vs placebo, respectively
- Bath Ankylosing Spondylitis Functional Index (BASFI) decreased (indicating improvement) significantly from baseline (p<0.001 in both trials)
  - BE MOBILE 1: –2.5 (standard error [SE]: 0.2) vs –1.0 (SE: 0.2), mean difference (MD): –1.5 (95% CI: –2.0, –1.0) bimekizumab vs placebo, respectively
  - BE MOBILE 2: –2.2 (SE: 0.1) vs –1.1 (SE: 0.2), MD: –1.1 (95% CI: –1.5, –0.6) bimekizumab vs placebo, respectively
- Nocturnal sleep pain decreased (indicating improvement) significantly from baseline (p<0.001 in both trials)
  - BE MOBILE 1: –3.6 (SE: 0.3) vs –1.7 (SE: 0.2), MD: –1.8 (95% CI: –2.4, –1.2) bimekizumab vs placebo, respectively
  - BE MOBILE 2: –3.3 (SE: 0.2) vs –1.9 (SE: 0.2), MD: –1.5 (95% CI: –2.0, –1.0) bimekizumab vs placebo, respectively
- Ankylosing Spondylitis Quality of Life (ASQoL) decreased (indicating improvement) significantly from baseline (p<0.001 in both trials)
  - BE MOBILE 1: –5.2 (SE: 0.4) vs –2.5 (SE: 0.4), MD: –2.6 (95% CI: –3.7, –1.6) bimekizumab vs placebo, respectively
  - BE MOBILE 2: –4.9 (SE: 0.3) vs –3.2 (SE: 0.3), MD: –1.5 (95% CI: –2.4, –0.7) bimekizumab

vs placebo, respectively

Bimekizumab-treated patients achieved high treatment outcomes (ASAS40) at week 16 or week 52 regardless of prior tumour necrosis factor alpha (TNF-α) inhibitor exposure (47)

- In patients with prior TNF-α inhibitor exposure, ASAS40 response rate at Week 16 with bimekizumab was higher in BE MOBILE 1 and BE MOBILE 2 (60% and 40.5%, respectively) compared with placebo (11.8% and 17.6%, respectively).
- In patients with no prior TNF-α inhibitor exposure, ASAS40 response rate at Week 16 was higher with bimekizumab (46.6% and 45.7%, respectively) compared with placebo (22.9% and 23.4%, respectively)

Long-term (52-week) data from BE MOBILE 1 and BE MOBILE 2 demonstrated that the response to bimekizumab treatment was maintained across the disease spectrum in efficacy endpoints relating to disease activity, physical function, pain, and QoL (Section B.3.6.2.2).

- ASAS40 response was maintained from Week 16 (BE MOBILE 1: 46.6%; BE MOBILE 2: 45.7%) to Week 52 (BE MOBILE 1: 60.9%; BE MOBILE 2: 58.4%)
- ASDAS-MI score further increased from Week 16 (BE MOBILE 1: 27.3%, BE MOBILE 2: 25.8% to Week 52 (BE MOBILE 1: 36.7%; BE MOBILE 2: 32.1)
- BASFI further decreased from Week 16 (BE MOBILE 1: –2.5; BE MOBILE 2: –2.2) to Week 52 (BE MOBILE 1: –3.0; BE MOBILE 2: –2.8)
- Nocturnal sleep pain further decreased from Week 16 (BE MOBILE 1: –3.6; BE MOBILE 2: –3.3) to Week 52 (BE MOBILE 1: –4.3; BE MOBILE 2: –4.1)
- ASQoL further decreased from Week 16 (BE MOBILE 1: –5.2; BE MOBILE 2: –4.9) to Week 52 (BE MOBILE 1: –5.9; BE MOBILE 2: –5.7)

The BE AGILE and BE AGILE 2 trials in AS demonstrated that the favourable efficacy and safety profile of bimekizumab was maintained over 156 weeks (Section B.3.10.2)

- >50% of patients achieved ASAS40 at all timepoints through weeks 48–156, and by week 156, 49% of the patient population had achieved ASDAS disease activity scores of <2.1, demonstrating the stringent disease control attained with bimekizumab (Section B.3.6.4).
- The most commonly reported adverse events (AE) with bimekizumab in the double-blind and overall periods in both trials were nasopharyngitis, upper respiratory tract infection, and bronchitis (Section B.3.10.2)

Two network meta-analyses (NMA) showed that bimekizumab was associated with either significantly improved or similar disease outcomes vs ixekizumab in predominantly b/tsDMARD-naïve patients with nr-axSpA or AS (Section B.3.9).

- In the absence of head-to-head data vs ixekizumab, an NMA was performed to assess the comparative relative efficacy in predominantly biologic/targeted synthetic disease modifying anti-rheumatic drug (b/tsDMARD)-naïve patients with nr-axSpA or AS.
- Bimekizumab was associated with significantly improved change from baseline BASDAI and BASFI vs ixekizumab in predominantly b/tsDMARD-naïve patients with nr-axSpA. For nr-axSpA, favourable results (no significant differences) were observed for the outcomes ASAS40, BASDAI50, or fatigue numerical rating scale (NRS). Importantly, in no comparisons were outcomes with bimekizumab statistically significantly worse than those for ixekizumab.
- In TNF-α experienced patients with AS, bimekizumab was associated with likely favourable (no significant differences) results for ASAS20, ASAS40, and BASFI compared with ixekizumab.
- The odds of discontinuation due to any reason; discontinuation due to AEs and serious adverse events were shown to be similar between bimekizumab and ixekizumab.
- The dual inhibition of IL-17A in addition to IL-17F with bimekizumab may therefore offer a promising treatment option for patients with axSpA, providing similar or improved disease outcomes vs 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 relevant comparators for the treatment of patients with axSpA. Taken together, the original clinical SLR and eight clinical SLR updates (including the January 2023 update) identified 341 publications for inclusion, reporting on 65 unique trials. A feasibility assessment was performed to determine which of the 65 unique randomised controlled trials (RCT) identified by the SLR were suitable for inclusion in the NMA. Of the 65 unique RCTs included in the SLR, 37 met the additional NMA eligibility criteria. 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 nr-axSpA and AS that are relevant to this submission are provided in Table 6.

Table 6: Overview of relevant clinical evidence informing the submission

Study	Submission evidence	Primary study reference(s)
BE MOBILE 1 (AS0010; NCT03928704) (140)	Primary efficacy evidence (Week 16; data cut-off date: 20th December 2021)	van der Heijde, 2023 (47) supplemented with the Week 52 CSR (141)
	Supporting long-term efficacy evidence (Week 52; data cut-off date:1st July 2022)	Baraliakos, 2022a (144), Baraliakos, 2022b (145), Gaffney, 2022 (146); supplemented with the Week 52 CSR (141)
	Safety evidence (Week 16; data cut-off date: 20th December 2021; Week 52; data cut-off date:1st July 2022)	van der Heijde et al 2023 (47); Baraliakos et al 2022 (144); supplemented with Week 52 CSR (141)
BE MOBILE 2 (AS0011; NCT03928743) (143)	Primary efficacy evidence (Week 16; data cut-off data16th November 2021)	van der Heijde, 2023(47) supplemented with the Week 52 CSR (142)
	Supporting long-term efficacy evidence (Week 52; data cut-off date: 31st May 2022)	Baraliakos, 2022a (144), Baraliakos, 2022b (145), Gaffney, 2022 (146); supplemented with Week 52 CSR (142)
	Safety evidence (Week 16; data cut-off data16th November 2021; Week 52; data cut-off date: 31st May 2022)	van der Heijde et al 2023 (47); Baraliakos et al 2022 (144); supplemented with Week 52 CSR (142)
BE AGILE (AS0008) (147)	Supporting long-term efficacy and safety evidence (Week 156); data cut-off date: 25th August 2020)	Baraliakos et al 2022 (147)
BE AGILE 2 (AS0009) (147)		

Abbreviations: CSR, clinical study report.

The primary sources of clinical efficacy evidence for bimekizumab in axSpA are the two Phase 3 RCTs, BE MOBILE 1 (nr-axSpA) (47, 140, 141), and BE MOBILE 2 (AS) (Table 7) (47, 142, 143). BE AGILE and BE AGILE 2 provide supporting long-term efficacy and safety evidence for bimekizumab in AS (147).

Table 7: Clinical effectiveness evidence – BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS)

Study	BE MOBILE 1 (AS0010) (NCT03928704) (140, 141)	BE MOBILE 2 (AS0011) (NCT03928743) (142, 143)
Study design	Phase 3, multicentre, randomised, double-blind, placebo-controlled trial	
Population	Adult patients (≥18 years, age at symptom onset <45 years) with nr-axSpA (meeting ASAS criteria (83, 84)) who had either failed to respond to two different NSAIDs or had a history of intolerance or contraindication to NSAID therapy Patients who had taken a TNF-α inhibitor must have experienced an inadequate response or have been intolerant to treatment.	Adult patients (≥18 years, age at symptom onset <45 years) with AS (meeting mNY criteria (40)) who had either failed to respond to two different NSAIDs or had a history of intolerance or a contraindication to NSAID therapy. Patients who had taken a TNF-α inhibitor must have experienced an inadequate response or have been intolerant to treatment.
Intervention(s)	Bimekizumab (prefilled 1 ml syringe, 160 mg/mL) SC Q4W	
Comparator(s)	Placebo (prefilled 1 ml syringe, 0.9% sodium chloride aqueous solution) SC Q4W	
Indicate if the trial supports the application for marketing authorisation	Yes	Yes

Reported outcomes specified in the decision problem	• ASAS40 at Week 16 (primary endpoint) and 52
	• ASAS40 in TNF-α inhibitor-naïve patients at Week 16 and 52
	• BASDAI CfB at Week 16 and 52
	• ASAS20 at Week 16 and 52
	• ASAS PR at Week 16 and 52
	• ASDAS-MI at Week 16 and 52
	• ASAS 5/6 at Week 16 and 52
	• BASFI CfB at Week 16 and 52
	• NSP CfB at Week 16 and 52
	• ASQoL CfB at Week 16 and 52
	• SF-36 PCS CfB at Week 16 and 52
	• BASMI CfB at Week 16 and 52
	• Non-ranked outcomes:
	  ○ ASDAS states at Week 16 and 52
	  ○ BASDAI50 at Week 16 and 52
	  ○ MASES index CfB at Week 16 and 52
	• AEs at Week 16 and 52	

All other reported outcomes	N/A	

Abbreviations: AE, adverse event; AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis International Society; ASAS20, Assessment of SpondyloArthritis International Society 20% response criteria; ASAS40, Assessment of SpondyloArthritis International Society 40% response criteria; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Disease Metrology Index; CfB, change from baseline; MASES, Maastricht Ankylosing Spondylitis Enthesitis; MI, major improvement; mNY, modified New York; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, non-steroidal anti-inflammatory drug; NSP, nocturnal spine pain; PCS, physical component summary; PR, partial remission; Q4W, every 4 weeks; SC, subcutaneous; SF-36, Short Form 36-Item Health Survey; TNF-α, tumour necrosis factor-alpha.

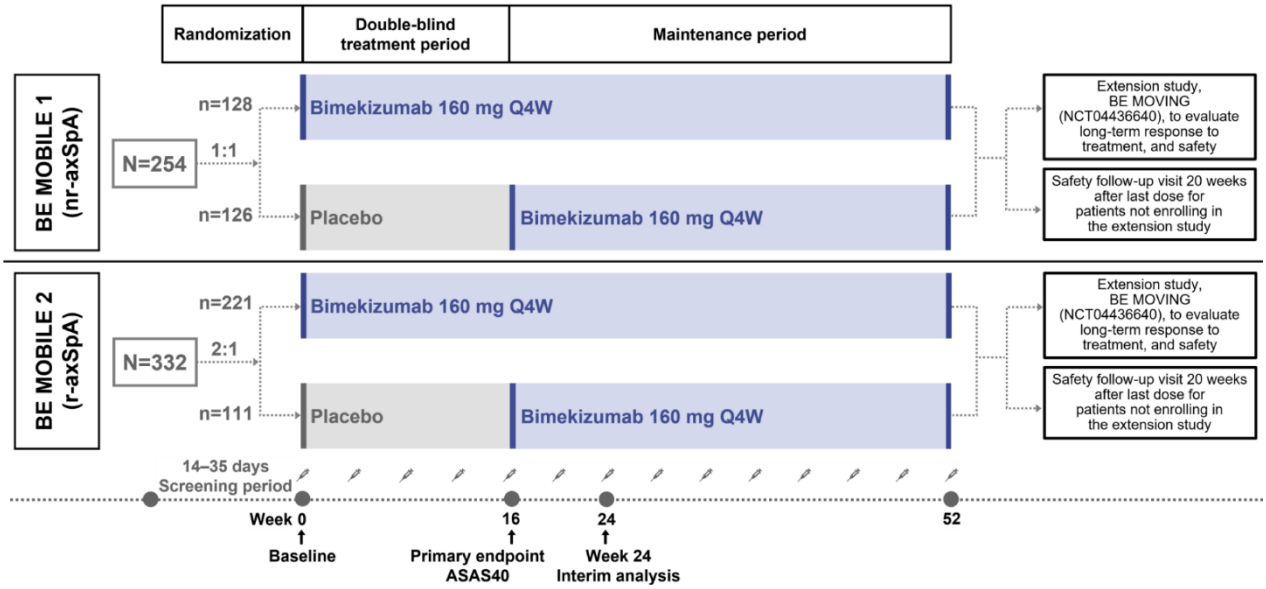
B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Primary evidence (BE MOBILE 1 and BE MOBILE 2)

B.3.3.1.1 *Trial design*

BE MOBILE 1 and BE MOBILE 2 consisted of a screening period lasting between 14 and 35 days, a 16-week double-blind period, and a 36-week maintenance period. At the end of the double-blind period, patients randomised to bimekizumab remained on their randomised dose and patients randomised to placebo were reallocated to receive bimekizumab after all Week 16 assessments had been completed. At Week 52, patients may have been eligible for enrolment in the open-label extension study (BE MOVING) (148). Patients who were ineligible for or elected not to participate in the extension study at Week 52 underwent a safety follow-up visit (20 weeks after final dose). A schematic of the study design is presented in Figure 2 and methods are provided in Table 8.

Figure 2: Study design of BE MOBILE 1 and BE MOBILE 2



Source: van der Heijde, 2023 (149)
Abbreviations: ASAS40, Assessment of Spondyloarthritis International Society 40%; nr-axSpA, non-radiographic axial spondyloarthritis; Q4W, every four weeks; r-axSpA, radiographic axial spondyloarthritis.

Table 8: Summary of trial methodology - BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS)

Trial name	BE MOBILE 1 (nr-axSpA) (140, 141)	BE MOBILE 2 (AS) (142, 143)
Location	95 centres from 14 countries across North America, Western Europe, Eastern Europe, and Asia	
Eligibility criteria	See Section B.3.3.1.2	
Randomisation	Treatment was stratified by region and by presence of sacroiliitis on MRI and elevated CRP: • MRI positive/CRP positive • MRI positive/CRP negative • MRI negative/CRP positive	Treatment was stratified by region and by TNF-α inhibitor exposure
Blinding	Patients and site personnel were blinded to the initially assigned treatment until study completion	
Study drugs	• Bimekizumab 160 mg/ml SC Q4W • Placebo SC Q4W (physiological saline)	
Permitted or prohibited, concomitant medications†	**Permitted:** analgesics, NSAID/COX-2 inhibitors, mild potency opioids, oral or topical corticosteroids, antidepressants, csDMARDs **Prohibited:** IM, IV, IA, or bursal corticosteroids, JAK inhibitors, TNF-α inhibitors, IL-17 inhibitors	
Pre-planned subgroups	Subgroup analyses of ASAS40 and ASDAS MI by TNF-α inhibitor exposure at Week 16	

†Any medication not listed here for rescue therapy must have been approved by the CRO medical monitor prior to starting that medication.
Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis International Society; ASAS40, Assessment of SpondyloArthritis International Society 40%; COX-2, cyclooxygenase; CRO, contract research organization; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IA, intra-articular; IM, intramuscular; IV, intravenous; JAK, Janus kinase; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, nonsteroidal anti-inflammatory drug; Q4W, every 4 weeks; SC, subcutaneous; TNF-α, tumour necrosis factor alpha.

B.3.3.1.2 *BE MOBILE 1 and BE MOBILE 2 eligibility criteria*

Key eligibility criteria are presented for BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS) in Table 9.

Table 9: Key eligibility criteria in BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS)

Inclusion criteria (140-143)	Exclusion criteria (140-143)
BE MOBILE 1 only • Adult-onset (male or females) axSpA meeting ASAS classification criteria (83, 84)† (not including family history and good response to NSAIDs) with inflammatory back pain for ≥3 months prior to screening • Must not have had sacroiliitis as defined by mNY criteria‡ • Have had objective inflammation (sacroiliitis on the screening MRI¶) **BE MOBILE 2 only** • Adult males or females with AS as per the mNY criteria with radiologic evidence (x-ray) and ≥3 months of symptoms (40) **BE MOBILE 1 and BE MOBILE 2** • Age at symptom onset <45 years • Have active disease as defined by BASDAI ≥4 and spinal pain ≥4 on a 0 to 10 NRS (from BASDAI Item 2) • Either failed to respond to two different NSAIDs at the maximum tolerated dose for 4 weeks or had a history of intolerance to, or a contraindication to, NSAIDs • Patients who had taken a TNF-α inhibitor must have experienced an inadequate response to previous treatment at an approved dose for ≥12 weeks or have been intolerant to treatment	**BE MOBILE 1 and BE MOBILE 2** • Female patients who were breastfeeding, pregnant, or planned to become pregnant during the study or within 20 weeks following the final dose • Previously participated in a bimekizumab clinical study who received ≥1 dose of study drug (including placebo) • Participation in another study of a systemic medication within 12 weeks or ≥5 half-lives (t½) prior to baseline, or currently participating in another study (except for patients who were screen failures in BE MOBILE 2) • Total ankylosis of the spine • Acute anterior uveitis within 6 weeks of baseline • Had received >1 TNF-α inhibitor and/or >2 additional non-TNF-α biological drugs, or any IL-17 biological drug at any time • Active infection (except common cold) within 14 days of baseline or a history of infections • Diagnosis of inflammatory conditions other than axSpA§

†Not including family history and good response to NSAIDs; ‡Bilateral ≥Grade 2; unilateral ≥Grade 3 based on central reading of AP pelvis or sacroiliac x-rays at screening or within 6 months prior to screening; ¶Defined by ASAS/OMERACT scoring via central reading (MRI+) AND/OR elevated CRP ≥1.2xULN (≥0.6mg/dL or ≥6.0 mg/L) at screening and no alternate diagnosis to explain MRI findings or elevated CRP; §Including but not limited to psoriatic arthritis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, and reactive arthritis. Patients with a diagnosis of Crohn's disease, ulcerative colitis, or other IBD were allowed if they had no active symptomatic disease at screening or baseline.

Abbreviations: AP, anterior-posterior; AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis International Society; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; IBD, inflammatory bowel disease; IL, interleukin; mNY, modified New York; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axial spondyloarthritis; NRS, numeric rating scale; NSAID, non-steroidal anti-inflammatory drug; OMERACT, Outcome Measures in Rheumatology Clinical Trials; TNF-α, tumour necrosis factor alpha; ULN upper limit of normal.

B.3.3.1.3 *Outcomes reported*

Table 10: Endpoints for BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS) (140-143)

Assessment	Description
Primary endpoint	
ASAS40 response at Week 16 and 52	• Based on the 4 main domains of the ASAS response criteria, an improvement of ≥40% ○ Absolute improvement of ≥2 units on a 0–10 NRS in ≥3 of the 4 following domains: PtGA, pain assessment (the Total Spinal Pain NRS score), physical function (measured by BASFI), inflammation (the mean of the BASDAI Q5/Q6, concerning morning stiffness intensity and duration) • And no worsening in the remaining domain
Ranked secondary endpoints	
ASAS40 response at Week 16 and 52 in TNF-α inhibitor-naïve patients	The ASAS40 response for patients with no prior TNF-α inhibitor experience
BASDAI total score at Week 16 and 52	Based on the BASDAI questionnaire comprising 6 questions (0–10 scale on a NRS) pertaining to the 5 major symptoms of AS: fatigue, spinal pain, joint pain/swelling, areas of localised tenderness (enthesitis, or inflammation of tendons and ligaments), morning stiffness duration, morning stiffness severity
ASAS20 response at Week 16 and 52	Based on the 4 main domains of the ASAS response criteria, an improvement of ≥20% and ≥1 unit on a scale of 10 in ≥3 of the 4 main domains and no worsening of ≥20% and ≥1 unit on a scale of 10 in the remaining domain
ASAS PR at Week 16 and 52	Value not ≥2 units in each of the 4 main domains of the ASAS response criteria on a scale of 10
ASDAS-MI at Week 16 and 52	The components comprising ASDAS are: total back pain (based on BASDAI Q2); duration of morning stiffness (based on BASDAI question 6); PtGA; peripheral pain/swelling (based on BASDAI question 3), each assessed on a NRS (0–10 units) and natural logarithm of hs-CRP (mg/L) +1, all multiplied by their weighting according to an established formula. ASDAS-MI was defined as a reduction (i.e. improvement) in ASDAS of ≥2.0 from baseline
ASAS5/6 response at Week 16 and 52	Improvement of ≥20% in ≥5 of all 6 domains of the ASAS response criteria
BASFI at Week 16 and 52	10 questions (0–10 scale on a NRS) designed to determine the degree of functional limitation in those patients with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patients' ability to cope with everyday life
NSP at Week 16 and 52	The pain experienced by AS patients was measured by the question *"How much pain of your spine due to spondylitis do you have at night?"* When responding, the patient was to consider the average amount of pain in the preceding week
ASQoL at Week 16 and 52	The ASQoL is a self-administered questionnaire designed to assess HRQoL in adult patients with AS. The ASQoL contains 18 items with a dichotomous yes/no response option. A single point is assigned for each "yes" response and no points for each "no" response resulting in overall scores that range from 0 (least severity) to 18 (highest severity).

Assessment	Description
SF-36 PCS at Week 16 and 52	The SF-36 PCS T-score is calculated using scores from the 8 SF-36 domains (Physical Functioning [10 items], Role Physical [4 items], Bodily Pain [2 items], General Health [5 items], Vitality [4 items], Social Functioning [2 items], Role Emotional [3 items], Mental Health [5 items]) and standardised with a mean (SD) of 50 in the general US population, where higher scores reflects higher physical ability and wellbeing
BASMI at Week 16 and 52	Uses the minimum number of clinically appropriate measurements that assess axial status, with the goal to define clinically significant changes in spinal movement; parameters include lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance, cervical rotation angle
Non-ranked secondary endpoints	
ASDAS states at Week 16 and 52	ASDAS components include: total back pain (based on BASDAI Q2); duration of morning stiffness (based on BASDAI question 6); PtGA; peripheral pain/swelling (based on BASDAI question 3), each assessed on a NRS (0–10 units) and natural logarithm of hs-CRP (mg/L) +1, all multiplied by their weighting according to an established formula.
BASDAI50 at Week 16 and 52	The BASDAI50 is defined as an improvement of ≥50% compared with baseline
SPARCC MRI SIJ at Week 16 and 52	A scoring system for assessing the sacroiliac joints based on STIR sequences. The sacroiliac joints are divided into four quadrants (upper iliac, lower iliac, upper sacral, and lower sacral). The presence of increased signal on STIR in each of these four quadrants is scored (either 0=normal signal or 1=increased signal). The maximum score for abnormal signal in the two sacroiliac joints of one coronal slice is therefore 8. Joints that include a lesion exhibiting intense signal are each given an additional score of 1 per slice. Each sacroiliac joint that includes a lesion demonstrating continuous increase signal of depth ≥1cm from the articular surface is also given an additional score of 1. The maximum score for a single coronal slice was 12. Scoring was repeated in each of six consecutive coronal slices, so that the total sacroiliac joints SPARCC MRI score ranged from 0–72.
FACIT-fatigue at Week 16 and 52	The FACIT-Fatigue© is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function
MASES index at Week 16 and 52	The MASES index measures the severity (i.e. intensity and extent) of enthesitis through the assessment of 13 entheses (bilateral costochondral 1, costochondral 7, anterior superior iliac spine, posterior iliac spine, iliac crest, and proximal insertion of the Achilles tendon sites, and the fifth lumbar vertebral body spinous process), each scored as 0 or 1 and then summed for a possible score of 0 to 13.
Safety	
AE	AEs are any untoward medical occurrence in a patient or clinical investigation study participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Abbreviations: AE, adverse event; AS, ankylosing spondylitis; ASAS20, Assessment of SpondyloArthritis International Society 20%; ASAS40, Assessment of SpondyloArthritis International Society 40%; ASAS5/6, Assessment of SpondyloArthritis International Society 5 out of 6 response criteria; ASAS PR, Assessment of SpondyloArthritis International Society partial remission; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score C-reactive protein; ASDAS-MI, Ankylosing Spondylitis Disease Activity Score major improvement; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Disease Metrology Index; CfB, change from baseline; HRQoL, health-related quality of life; hs-CRP, high sensitivity C-reactive protein; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MCS; NRS, numeric rating scale; PCS, physical component summary; PtGA, Patient's Global Assessment of Disease Activity; PhGADA, Physician's Global Assessment of Disease Activity; SD, standard deviation; SF-36, Short Form 36-Item Health Survey; SPARCC, Spondyloarthritis Research Consortium of Canada; TNF-α, tumour necrosis factor alpha.

B.3.3.2 Supporting evidence (BE AGILE and BE AGILE 2)

B.3.3.2.1 *Trial design*

The BE AGILE study was a 48-week randomised, parallel-group, Phase 2b, dose-ranging study, double-blind to Week 12, then dose-blind to Week 48. BE AGILE was conducted at 74 sites across 10 countries in Europe and the US. Patients who completed 48 weeks of treatment were eligible to enrol in the open-label extension (BE AGILE 2; NCT03355573) for an additional 204 weeks of treatment, with a subsequent safety visit 20 weeks after the last dose. BE AGILE 2 was conducted at 50 sites across the same 10 countries. The data presented represents bimekizumab treatment up to week 156, with 5 year data due end of 2023.

At baseline, patients were randomised 1:1:1:1:1 to receive subcutaneous bimekizumab 16 mg, 64 mg, 160 mg, or 320 mg or placebo every 4 weeks (Q4W). At Week 12, patients initially randomised to bimekizumab 16 mg, 64 mg, or placebo were re-randomised 1:1 to bimekizumab 160 mg or 320 mg Q4W through Week 48, while patients initially randomised to bimekizumab 160 mg or 320 mg continued their dosing to Week 48. All patients in the open-label extension (BE AGILE 2) received open-label bimekizumab 160 mg Q4W, regardless of their prior dosing regimen.

Full methods are presented in Appendix .

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

B.3.4.1.1 *BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS)*

The statistical analyses in BE MOBILE 1 and BE MOBILE 2 are summarised in Table 11.

Table 11: Statistical analysis in BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS)

	BE MOBILE 1 (141)	BE MOBILE 2 (142)
Analysis sets	• RS: All randomised patients • SS: The SS consisted of all randomised patients who received ≥1 dose of study treatment.	
Statistical analysis of primary and ranked secondary endpoints	• Analysis of the primary and secondary endpoints was based on the RS • A fixed sequence testing procedure was applied for the primary endpoint and ranked secondary endpoints; the testing procedure accounted for multiplicity and controls the family-wise type I error rate at alpha=0.05 (2-sided) • For binary efficacy endpoints, the null hypothesis was that the conditional OR=1; for continuous efficacy endpoints, the null hypothesis was that there was no difference between treatment groups Statistical testing of an endpoint could be investigated only if the null hypothesis for the previous endpoint had been rejected	
	• Sequential testing procedure of primary and key secondary efficacy endpoints • H1: ASAS40 response at Week 16 superior to placebo ○ H2: CfB BASDAI at Week 16 superior to placebo ○ H3: ASAS20 response at Week 16 superior to placebo ○ H4: ASAS PR at Week 16 superior to placebo ○ H5: ASDAS-MI at Week 16 superior to placebo ○ H6:ASAS5/6 response at Week 16 superior to placebo ○ H7: CfB BASFI at Week 16 superior to placebo ○ H8: CfB nocturnal spinal pain at Week 16 superior to placebo ○ H9: CfB ASQoL at Week 16 superior to placebo ○ H10: CfB PCS SF-36 at Week 16 superior to placebo	• Sequential testing procedure of primary and key secondary efficacy endpoints ○ H1: ASAS40 response at Week 16 superior to placebo ○ H2: ASAS40 response at Week 16 superior to placebo – TNF-α inhibitor-naïve ○ H3: ASAS20 response at Week 16 superior to placebo ○ H4: CfB BASDAI at Week 16 superior to placebo ○ H5: ASAS PR at Week 16 superior to placebo ○ H6: ASDAS-MI at Week 16 superior to placebo ○ H7: ASAS5/6 response at Week 16 superior to placebo ○ H8: CfB BASFI at Week 16 superior to placebo ○ H9: CfB nocturnal spinal pain at Week 16 superior to placebo ○ H10: CfB ASQoL at Week 16 superior to placebo ○ H11: CfB PCS SF-36 at Week 16 superior to placebo ○ H12: CfB BASMI at Week 16 superior to placebo

	BE MOBILE 1 (141)	BE MOBILE 2 (142)
Statistical analysis of safety endpoints	Safety endpoints were analysed on the SS	
Sample size and power calculation	Sample sizes were calculated using a 2-sided 2-sample Chi-square test with continuity correction • Primary endpoint: the test for detecting statistical superiority of bimekizumab (n=120) versus placebo (BE MOBILE 1: n=120 and n=120, respectively, BE MOBILE 2: n=200 and n=100, respectively) based on ASAS40 response at Week 16 was powered with 90% • Secondary endpoints in the hierarchical testing: All power calculations for continuous endpoints were performed using a 2-sided 2-group Satterthwaite t-test • All sample size and power calculations were performed at a significance level of 0.05 in a 2-sided test	
Subgroup analysis	Subgroup analyses of ASAS40 and ASDAS MI by TNF-α inhibitor exposure at Week 16	

†IPDs were predefined and patients with IPDs were evaluated during ongoing data cleaning meetings prior to unblinding of the data. Exclusions from the FAS were considered IPDs that also resulted in exclusion from the PPS. Additional exclusions from the PPS due to a protocol-permitted decrease in dosing or dosing frequency of axSpA background medication due to intolerance/AE/side effects may have also been possible in case a potential impact on the primary endpoint cannot be excluded.
Abbreviations: AE, adverse event; ASAS40, Assessment of SpondyloArthritis International Society 40%; axSpA, axial spondyloarthritis; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; IPD, important protocol deviation; MI, multiple imputation; MRI, magnetic resonance imaging; NRI, non-responder imputation; Q4W, every 4 weeks; RS, randomised set; SS, safety set; TNF-α, tumour necrosis factor alpha.

B.3.4.2 Patient disposition and baseline characteristics

B.3.4.2.1 *BE MOBILE 1 and BE MOBILE 2 patient disposition*

In BE MOBILE 1, patients were stratified by region, and by the presence of sacroiliitis on MRI and elevated CRP to ensure balanced treatment allocation across the three MRI/CRP classification levels. A total of 254 patients were randomised to the double-blind period: 128 patients to the bimekizumab group and 126 patients to the placebo group.

In BE MOBILE 2, patients were randomised 2:1 (stratified by region and prior TNF-α inhibitor experience) to bimekizumab or placebo. A total of 332 patients were randomised to the double-blind period: 221 patients to the bimekizumab group and 111 patients to the placebo group. A summary of patient disposition is presented in Table 12.

Table 12: BE MOBILE 1 and BE MOBILE 2 patient disposition (randomised set)

	BE MOBILE 1			BE MOBILE 2		
	Bimekizumab 160 mg Q4W n=128	Placebo n=126	All patients N=254	Bimekizumab 160 mg Q4W n=221	Placebo n=111	All patients N=332
Started double-blind period	128 (100)	126 (100)	254 (100)	221 (100)	111 (100)	332 (100)
Completed double-blind period	126 (98.4)	118 (93.7)	244 (96.1)	213 (96.4)	109 (98.2)	322 (97.0)
Discontinued during double-blind period	2 (1.6)	8 (6.3)	10 (3.9)	8 (3.6)	2 (1.8)	10 (3.0)
Primary reason for study discontinuation						
AE	1 (0.8)	3 (2.4)	4 (1.6)	3 (1.4)	0	3 (0.9)
Lack of efficacy	0	1 (0.8)	1 (0.4)	1 (0.5)	0	1 (0.3)
Withdrawal by patient	0	4 (3.2)	4 (1.6)	3 (1.4)	1 (0.9)	4 (1.2)
Other	1 (0.8)	0	1 (0.4)	1 (0.5)	1 (0.9)	2 (0.6)

Source: UCB Data on file (150); UCB Data on file (151)
Abbreviations: AE, adverse event; Q4W, every four weeks.

B.3.4.3 BE MOBILE 1 and BE MOBILE 2 baseline characteristics

In BE MOBILE 1 and BE MOBILE 2, the treatment groups were generally well balanced with respect to nr-axSpA/AS-related and other baseline characteristics (Table 13).

In BE MOBILE 1, the mean age of all enrolled patients was 39.4 years (range of 18 to 76 years). Overall, there was a higher proportion of male than female patients (54.3% vs 45.7%, respectively), and most patients were white (86.2%). For each treatment group, the number of patients in the MRI+/CRP- stratification level was slightly higher (41.7%) compared with MRI+/CRP+ (31.9%) and MRI-/CRP+ (26.4%) stratification levels. The mean time since first diagnosis and was 3.60 years (range: 0.1 to 31.3 years) and the mean time since first nr-axSpA symptoms was 9.02 years (range: 0.4 to 45.1 years). In total, 10.6% of patients had received prior TNF-α inhibitor therapy.

In BE MOBILE 2, the mean age of all enrolled patients was 40.4 years (range of 19 to 80 years). Overall, there was a higher proportion of male than female patients (72.3% vs 27.7%, respectively), and most patients were white (80.4%). For each treatment group, the proportions of patients enrolled in each region. The mean time since first AS diagnosis was 6.39 years (range: 0.1 to 41.0 years) and the time since first AS symptoms was 13.46 years (range: 0.4 to 59.1 years). In total, 16.3% of patients had received prior TNF-α inhibitor therapy, the proportions of patients in each treatment group with previous TNF-α inhibitor exposure were similar.

Table 13: BE MOBILE 1 and BE MOBILE 2 patient baseline demographics (safety set)

Variable	BE MOBILE 1 (nr-axSpA)			BE MOBILE 2 (AS)		
	Bimekizumab 160 mg Q4W n=128	Placebo n=126	All patients N=254	Bimekizumab 160 mg Q4W n=221	Placebo n=111	All patients N=332
Age (years)						
Mean (SD)	39.5 (11.1)	39.4 (11.8)	39.4 (11.5)	41.0 (12.1)	39.2 (12.6)	40.4 (12.3)
Gender, n (%)						
Female	55 (43.0)	61 (48.4)	116 (45.7)	61 (27.6)	31 (27.9)	92 (27.7)
Region, n (%)§						
Asia	15 (11.7)	13 (10.3)	28 (11.0)	21 (18.9)	40 (18.1)	61 (18.4)
Eastern Europe	73 (57.0)	71 (56.3)	144 (56.7)	55 (49.5)	108 (48.9)	163 (49.1)
North America	9 (7.0)	9 (7.1)	18 (7.1)	3 (2.7)	6 (2.7)	9 (2.7)
Western Europe	31 (24.2)	33 (26.2)	64 (25.2)	32 (28.8)	67 (30.3)	99 (29.8)
Time since first diagnosis of axSpA (BE MOBILE 1) or AS (BE MOBILE 2) (years)						
Mean (SD)	3.7 (6.2)	3.6 (5.4)	3.6 (5.8)	6.7 (8.3)	5.7 (6.9)	6.2 (7.9)
Time since first symptoms of nr-axSpA (BE MOBILE 1) or AS (BE MOBILE 2) (years)						
Mean (SD)	9.1 (8.7)	9.0 (9.0)	9.02 (8.83)	14.2 (11.0)	11.91 (8.6)	13.46 (10.31)
BMI (kg/m^2)†						
Mean (SD)	27.2 (6.0)	27.7 (5.5)	27.4 (5.8)	26.8 (5.7)	27.1 (5.8)	26.9 (5.6)
MRI/CRP classification¶						
MRI+/CRP+	39 (30.5)	39 (31.0)	78 (30.7)	–	–	–
MRI+/CRP-	53 (41.4)	56 (44.4)	109 (42.9)	–	–	–
MRI-/CRP+	36 (28.1)	31 (24.6)	67 (26.4)	–	–	–
MRI status at screening						
Positive	92 (71.9)	95 (75.4)	187 (73.6)	–	–	–
hs-CRP status at screening						
Positive (≥1.2 ULN)	75 (58.6)	70 (55.6)	145 (57.1)	–	–	–
HLA-B27						
Positive	103 (80.5)	94 (74.6)	197 (77.6)	191 (86.4)	93 (83.8)	284 (85.5)
Past anti-TNF therapy						
Yes	10 (7.8)	17 (13.5)	27 (10.6)	37 (16.7)	17 (15.3)	54 (16.3)
Current NSAID therapies‡‡						
Yes	97 (75.8)	93 (73.8)	190 (74.8)	180 (81.4)	180 (81.4)	265 (79.8)
Current csDMARDs‡‡						
Yes	30 (23.4)	32 (25.4)	62 (24.4)	47 (21.3)	19 (17.1)	66 (19.9)

Variable	BE MOBILE 1 (nr-axSpA)			BE MOBILE 2 (AS)		
	Bimekizumab 160 mg Q4W n=128	Placebo n=126	All patients N=254	Bimekizumab 160 mg Q4W n=221	Placebo n=111	All patients N=332
Current oral corticosteroid use‡‡						
Yes	7 (5.5)	14 (11.1)	21 (8.3)	15 (6.8)	8 (7.2)	23 (6.9)

Source: van der Heijde, 2023 (47); UCB Data on file (150); UCB Data on file (151)
†BMI was derived based on the height and weight variables collected in the database; ‡Patients were categorised based on the stratum within which they were randomised via the IXRS; ¶Patients categorised by the stratum to which they belong, which may differ from the stratum they were randomised to;. Patients with no evaluable MRI sacroiliitis imaging result at screening or patients classified in MRI-/CRP- were assigned under the missing MRI/CRP category; §Turkey was included in the Asian region; ††Radiologic criterion referred to sacroiliitis grade ≥2 bilaterally or grade 3 to 4 unilaterally; ‡‡Current medications were medications concomitant at baseline.
Abbreviations: AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; BMI, body mass index; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HLA-B27, human leukocyte antigen B27; hs-CRP, high-sensitivity C reactive protein; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, nonsteroidal anti-inflammatory drug; Q4W, every 4 weeks; SD, standard deviation; TNF, tumour necrosis factor; ULN, upper limit of normal.

B.3.4.3.1 *Baseline efficacy characteristics*

Baseline efficacy characteristics were well balanced across treatment groups, consistent with the study's inclusion criteria and reflective of active disease (Table 14).

Table 14: Baseline efficacy characteristics (safety set)

Variable	BE MOBILE 1 (nr-axSpA)			BE MOBILE 2 (AS)		
	Bimekizumab 160 mg Q4W n=128	Placebo n=126	All Patients N=254	Bimekizumab 160 mg Q4W n=221	Placebo n=111	All patients N=332
PtGA†						
Mean (SD)	7.1 (1.9)	6.9 (1.9)	7.0 (1.9)	6.6 (2.0)	6.7 (1.8)	6.7 (1.9)
Total spinal pain NRS†						
Mean (SD)	7.3 (1.5)	7.1 (1.6)	7.2 (1.5)	7.1 (1.6)	7.2 (1.2)	7.2 (1.5)
BASFI score†						
Mean (SD)	5.5 (2.2)	5.3 (2.3)	5.43 (2.26)	5.3 (2.2)	5.2 (2.0)	5.24 (2.13)
BASDAI total score						
Mean (SD)	6.9 (1.2)	6.7 (1.3)	6.80 (1.27)	6.5 (1.3)	6.5 (1.3)	6.47 (1.32)

Source: van der Heijde, 2023 (47).
†This was part of the primary outcome measure.
Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; nr-axSpA, non-radiographic axial spondyloarthritis; NRS, numeric rating scale; PTGA, Patient's Global Assessment of Disease Activity; Q4W, every 4 weeks; SD, standard deviation.

B.3.4.3.2 *Prior and concomitant diseases*

In BE MOBILE 1, 93.7% of patients in the safety set reported a previous and ongoing medical condition at baseline. The most frequently reported conditions/diseases at baseline were musculoskeletal and connective tissue disorders (70.5%), infection and infestations (33.1%), and metabolism and nutrition disorders (27.2%). The incidences of previous or ongoing medical conditions at baseline were generally similar between treatment groups. The most frequently reported peripheral and extra-articular manifestations at baseline and screening were peripheral arthritis (40.9%), enthesitis (32.7%, including heel enthesitis [26.0%]), and uveitis (15.7%).

In BE MOBILE 2, 91.9% of patients in the safety set reported a previous and ongoing medical condition at baseline. The most frequently reported conditions/diseases at baseline were musculoskeletal and connective tissue disorders (59.9%), metabolism and nutrition disorders (29.5%), and gastrointestinal disorders (27.1%). The incidences of previous or ongoing medical conditions at baseline were generally similar between treatment groups. The most frequently reported peripheral and extra-articular manifestations at baseline and screening were peripheral arthritis (36.7%), enthesitis (26.5%, including heel enthesitis [18.7%]), and uveitis (17.2%).

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 trials

B.3.6.1 BE MOBILE 1 and BE MOBILE 2 primary endpoint: ASAS40 response at Week 16

In BE MOBILE 1 and BE MOBILE 2, ASAS40 response rates were significantly higher in the bimekizumab group compared with placebo at Week 16 (BE MOBILE 1: 47.7% vs 21.4%, BE MOBILE 2: 44.8% vs 22.5%, respectively; both p<0.001) (Table 15). Results of supportive analyses of the primary efficacy endpoints in BE MOBILE 1 and BE MOBILE 2 were consistent with the primary analysis, and response rates were higher with bimekizumab vs placebo for all individual components of ASAS40 (subgroup analyses of ASAS40 by TNF-α inhibitor exposure are presented in Section B.3.7.1).

Table 15: BE MOBILE 1 and BE MOBILE 2 ASAS40 response rate at Week 16 (randomised set [NRI])

	BE MOBILE 1 (nr-axSpA)		BE MOBILE 2 (AS)	
	Bimekizumab 160 mg Q4W n=128	Placebo n=126	Bimekizumab 160 mg Q4W n=221	Placebo n=111
Number of responders, n (%)	61 (47.7)	27 (21.4)	99 (44.8)	25 (22.5)
Difference vs placebo (95% CI)	27.0 (15.6, 38.4)	–	21.8 (11.4, 32.1)	–
p-value	<0.001	–	<0.001	–

Source: van der Heijde, 2023 (47).
Abbreviations: ASAS40, Assessment in SpondyloArthritis International Society 40%; CI, confidence interval; CRP, C-reactive protein; MRI, magnetic resonance imaging; NRI, non-responder imputation; Q4W, every 4 weeks.

B.3.6.2 BE MOBILE 1 and BE MOBILE 2: Ranked secondary endpoints

B.3.6.2.1 *Week 16 (primary analysis)*

All ranked secondary endpoints for both BE MOBILE 1 and BE MOBILE 2 were statistically significant at Week 16 in favour of bimekizumab versus placebo (Table 16). Note that for BE MOBILE 1, ASAS40 in TNF-α inhibitor-naïve patients and BASMI CfB were not part of the sequential hierarchy testing (i.e. not ranked endpoints), but are included in Table 16 to facilitate comparisons. Results of supportive analyses of the secondary efficacy endpoints were consistent with the primary analysis. The effect of bimekizumab on all ranked secondary endpoints in BE MOBILE 1 and BE MOBILE 2 was maintained through to Week 52 (Table 17).

Table 16: Summary of ranked secondary efficacy analysis results based on the predefined sequential testing sequence at Week 16 (randomised set)

	BE MOBILE 1 (nr-axSpA)				BE MOBILE 2 (AS)			
Endpoint	**Bimekizumab 160 mg Q4W n=128**	**Placebo n=126**	**Odds ratio/ difference‡ (95% CI)**	**p-value**	**Bimekizumab 160 mg Q4W n=221**	**Placebo n=111**	**Odds ratio/ difference‡ (95% CI)**	**p-value**
ASAS40 in TNF-α inhibitor-naïve patients, n (%)†	55 (46.6)	25 (22.9)	3.08 (1.71, 5.54)	0.0002	84 (45.7)	22 (23.4)	22.2 (10.6, 33.9)	<0.001
ASAS40 in TNF-α inhibitor IR [NRI], n (%)¶	6 (60.0)	2 (11.8)	–	–	15 (40.5)	3 (176)	–	–
BASDAI CfB [MI], mean (SE)	–3.1 (0.20)	–1.5 (0.2)	–1.5‡ (–2.0, –1.0)	<0.001	–2.9 (0.1)	–1.9 (0.2)	–1.0‡ (–1.5, –0.6)	<0.001
ASAS20 [NRI], n (%)	88 (68.8)	48 (38.1)	31.4 (19.5, 43.2)	<0.001	146 (66.1)	48 (43.2)	24.0 (12.8, 35.2)	<0.001
ASAS PR [NRI], n (%)	33 (25.8)	9 (7.1)	19.4 (10.1, 28.7)	<0.001	53 (24.0)	8 (7.2)	14.7 (7.3, 22.1)	<0.001
ASDAS-MI [NRI], n (%)	35 (27.3)	9 (7.1)	19.0 (10.7, 27.2)	<0.001	57 (25.8)	6 (5.4)	18.6 (10.9, 26.3)	<0.001
ASAS 5/6 [NRI], n (%)	58 (45.3)	26 (20.6)	25.7 (14.1, 37.3)	<0.001	109 (49.3)	21 (18.9)	29.3 (19.2, 39.3)	<0.001
BASFI CfB [MI], mean (SE)	–2.5 (0.2)	–1.0 (0.2)	–1.5‡ (–2.0, –1.0)	<0.001	–2.2 (0.1)	–1.1 (0.2)	–1.1‡ (–1.5, –0.6)	<0.001
NSP CfB [MI], mean (SE)	–3.6 (0.3)	–1.7 (0.2)	–1.8‡ (–2.4, –1.2)	<0.001	–3.3 (0.2)	–1.9 (0.2)	–1.5‡ (–2.0, –1.0)	<0.001
ASQoL CfB [MI], mean (SE)	–5.2 (0.4)	–2.5 (0.4)	–2.6‡ (–3.7, –1.6)	<0.001	–4.9 (0.3)	–3.2 (0.3)	–1.5‡ (–2.4, –0.7)	<0.001
SF-36 PCS CfB [MI], mean (SE)	9.5 (0.7)	5.5 (0.7)	4.0 (2.1, 5.8)	<0.001	9.3 (0.6)	5.9 (0.8)	3.4‡ (1.7, 5.1)	<0.001
BASMI CfB [MI], mean (SE)§	–0.4 (0.1)	–0.1 (0.1)	–	–	–0.5 (0.1)	–0.2 (0.1)	–0.3‡ (–0.5, –0.1)	0.006

Source: Baraliakos, 2022a (145); Baraliakos, 2022b (144) van der Heijde, 2023 (47);
†ASAS40 in the TNF-α inhibitor naïve population was not a ranked endpoint in BE MOBILE 1; ‡difference vs placebo; ¶placebo n=17, BE MOBILE 1 bimekizumab, n=10, BE MOBILE 2 bimekizumab n=37; §BASMI was not a ranked endpoint for BE MOBILE 1.
Abbreviations: AS, ankylosing spondylitis; ASAS20, Assessment of SpondyloArthritis International Society 20%; ASAS40, Assessment of SpondyloArthritis International Society 50%; ASAS5/6, Assessment of SpondyloArthritis International Society 5 out of 6 criteria; ASAS PR, Assessment of SpondyloArthritis International Society partial remission; ASDAS-MI, Ankylosing Spondylitis Disease Activity Score major improvement; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Disease Metrology Index; CfB, change from baseline; IR, inadequate responders; MI, multiple imputation; nr-axSpA, non-radiographic axial spondyloarthritis; NRI, non-responder imputation; NSP, nocturnal spine pain; PCS, physical component summary; Q4W, every 4 weeks; SE, standard error; SF-36, Short-Form 36-item Health Survey; TNF-α, tumour necrosis factor alpha.

B.3.6.2.2 *Week 52 (long-term supporting analysis)*

Table 17: Summary of ranked secondary efficacy analysis results at Week 52 (randomised set)

	Be MOBILE 1 (nr-axSpA)		BE MOBILE 2 (AS)	
Endpoint	**Bimekizumab 160 mg Q4W n=128**	**Placebo to bimekizumab (Week 16 switch) n=126**	**Bimekizumab 160 mg Q4W n=221**	**Placebo to bimekizumab (Week 16 switch) n=111**
ASAS40 [NRI], n (%)	78 (60.9)	64 (50.8)	129 (58.4)	76 (68.5)
ASAS40 in TNF-α inhibitor naïve [NRI], n (%)	73 (61.9)†	58 (53.2)‡	108 (58.7)¶	67 (71.3)§
ASAS40 in TNF-α inhibitor IR§§ [NRI], n (%)	5 (50.0)††	6 (35.3)‡‡	21 (56.8)¶¶	9 (52.9)†††
BASDAI CfB [MI], mean (SE)	–3.9 (0.2)	–3.5 (0.2)	–3.6 (0.1)	–4.0 (0.2)
ASAS20 [NRI], n (%)	94 (73.4)	88 (69.8)	158 (71.5)	89 (80.2)
ASAS PR [NRI], n (%)	38 (29.7)	38 (30.2)	66 (29.9)	41 (36.9)
ASDAS-MI [NRI], n (%)	47 (36.7)	37 (29.4)	71 (32.1)	49 (44.1)
ASAS 5/6 [NRI], n (%)	71 (55.5)	65 (51.6)	124 (56.1)	74 (66.7)
BASFI CfB [MI], mean (SE)	–3.0 (0.2)	–2.6 (0.2)	–2.8 (0.1)	–2.8 (0.2)
NSP CfB [MI], mean (SE)	–4.3 (0.3)	–4.1 (0.2)	–4.1 (0.2)	–4.6 (0.3)
ASQoL CfB [MI], mean (SE)	–5.9 (0.4)	–5.3 (0.4)	–5.7 (0.3)	–5.6 (0.4)
SF-36 PCS CfB [MI], mean (SE)	12.2 (0.9)	11.4 (0.9)	12.0 (0.6)	12.3 (0.9)
BASMI CfB [MI], mean (SE)	–0.6 (0.1)	–0.4 (0.1)	–0.7 (0.1)	–0.7 (0.1)

Source: Baraliakos, 2022 (144)
†n=118; ‡n=109; ¶n=184; §n=94; ††n=10; ‡‡n=17; ¶¶n=37; §§Patients received maximum of one TNFi; †††n=17.
Abbreviations: ASAS20, Assessment of SpondyloArthritis International Society 20%; ASAS40, Assessment of SpondyloArthritis International Society 50%; ASAS5/6, Assessment of SpondyloArthritis International Society 5 out of 6 criteria; ASAS PR, Assessment of SpondyloArthritis International Society partial remission; ASDAS-MI, Ankylosing Spondylitis Disease Activity Score major improvement; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Disease Metrology Index; CfB, change from baseline; MI, multiple imputation; NRI, non-responder imputation; PCS, physical component summary; SE, standard error; SF-36, Short-Form 36-item Health Survey; TNF-α, tumour necrosis factor alpha.

B.3.6.3 Non-ranked secondary endpoints

B.3.6.3.1 *BASDAI50*

In BE MOBILE 1, BASDAI50 response rate was higher (indicating an improvement) with bimekizumab (46.9%) compared with placebo (21.4%) at Week 16 (Table 18). At Week 52, response rates further increased (53.9%) with bimekizumab and had also increased in patients who switched from placebo to bimekizumab at Week 16 (49.2%). In BE MOBILE 2, BASDAI50 response rate was higher in the bimekizumab group (46.6%) compared with the placebo group (26.1%) at Week 16. At Week 52, BASDAI50 response rates further increased (53.8%) in the bimekizumab group, and had also increased in patients who switched from placebo to bimekizumab at Week 16 (62.2%) (Table 18).

Table 18: BASDAI50 response rate by visit (randomised set)

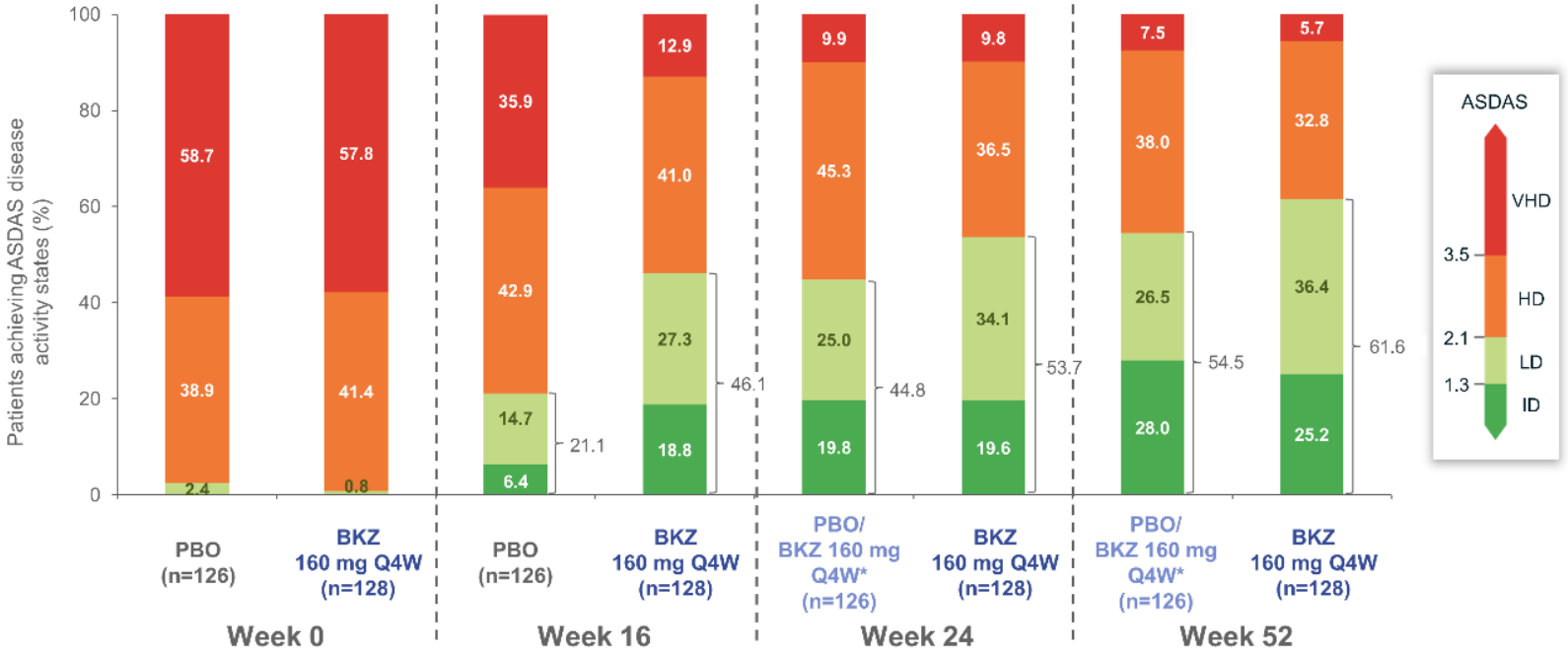
BASDAI50, n (%)	BE MOBILE 1 (nr-axSpA)		BE MOBILE 2 (AS)	
	Bimekizumab 160 mg Q4W N=128	Placebo to bimekizumab (Week 16 switch) N=126	Bimekizumab 160 mg Q4W N=221	Placebo to bimekizumab (Week 16 switch) N=111
Week 16	60 (46.9)	27 (21.4)	103 (46.6)	29 (26.1)
Week 52†	69 (53.9)	62 (49.2)	119 (53.8)	69 (62.2)

Source: Gaffney, 2022 (146).
†Switch group, patients switched from placebo to bimekizumab at Week 16.
Abbreviations: AS, ankylosing spondylitis; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50%; nr-axSpA, non-radiographic axial spondyloarthritis; Q4W, every 4 weeks.

B.3.6.3.2 *ASDAS states*

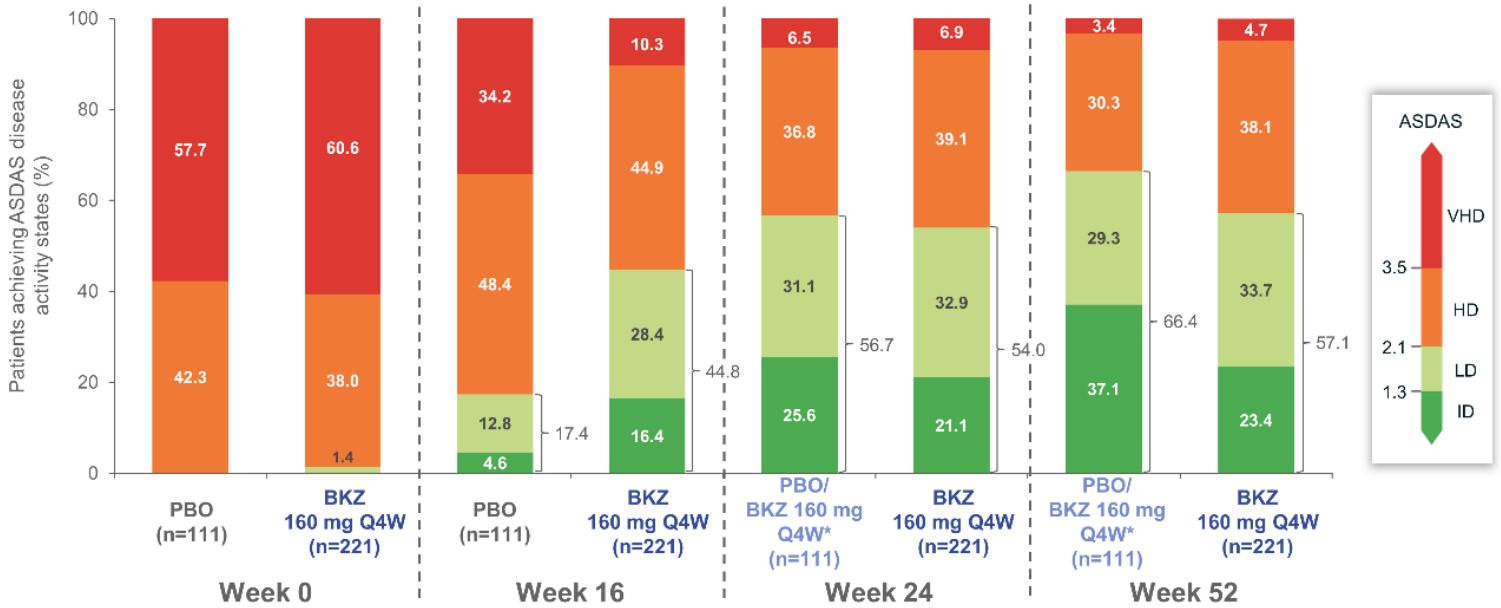
In BE MOBILE 1 and BE MOBILE 2, a higher proportion of patients achieved ASDAS <1.3 and ≥1.3 to <2.1 ASDAS (indicating improvement, achievement of ASDAS <2.1 is the current goal of treatment (34)) with bimekizumab compared with placebo between baseline and Week 16 (Figure 3 and Figure 4). The response was maintained to Week 52 in the bimekizumab groups. In the patients who switched from placebo to bimekizumab, the proportion of patients achieving ASDAS <1.3 and ≥1.3 to <2.1 ASDAS increased from Week 16 to Week 24, and was maintained to Week 52.

Figure 3: ASDAS status over time in BE MOBILE 1 (nr-axSpA) (randomised set [MI])



Source: Baraliakos, 2022 (145).
Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; BKZ, bimekizumab; HD, high disease; ID, inactive disease; LD, low disease; MI, multiple imputation; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; Q4W, every 4 weeks; VHD, very high disease.

Figure 4: ASDAS status over time in BE MOBILE 2 (AS) (randomised set [MI])



Source: Baraliakos, 2022 (145).
Abbreviations: AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BKZ, bimekizumab; HD, high disease; ID, inactive disease; LD, low disease; MI, multiple imputation; PBO, placebo; Q4W, every 4 weeks; VHD, very high disease.

B.3.6.3.3 *ASDAS CRP*

In BE MOBILE 1, the decrease (indicating improvement) from baseline in ASDAS CRP in the bimekizumab group (–1.5) was greater compared with the placebo group (–0.6) at Week 16. At Week 52, ASDAS CRP further decreased (–1.8) with bimekizumab and had also decreased in patients who switched from placebo to bimekizumab at Week 16 (–1.6). In BE MOBILE 2, the decrease from baseline in ASDAS CRP with bimekizumab (–1.4) was greater compared with placebo (–0.7) at Week 16. At Week 52, ASDAS CRP in the bimekizumab group further decreased (–1.7) and had also decreased in patients who switched from placebo to bimekizumab at Week 16 (–1.9) (Table 19).

Table 19: ASDAS-CRP change from baseline in BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS) (randomised set [MI])

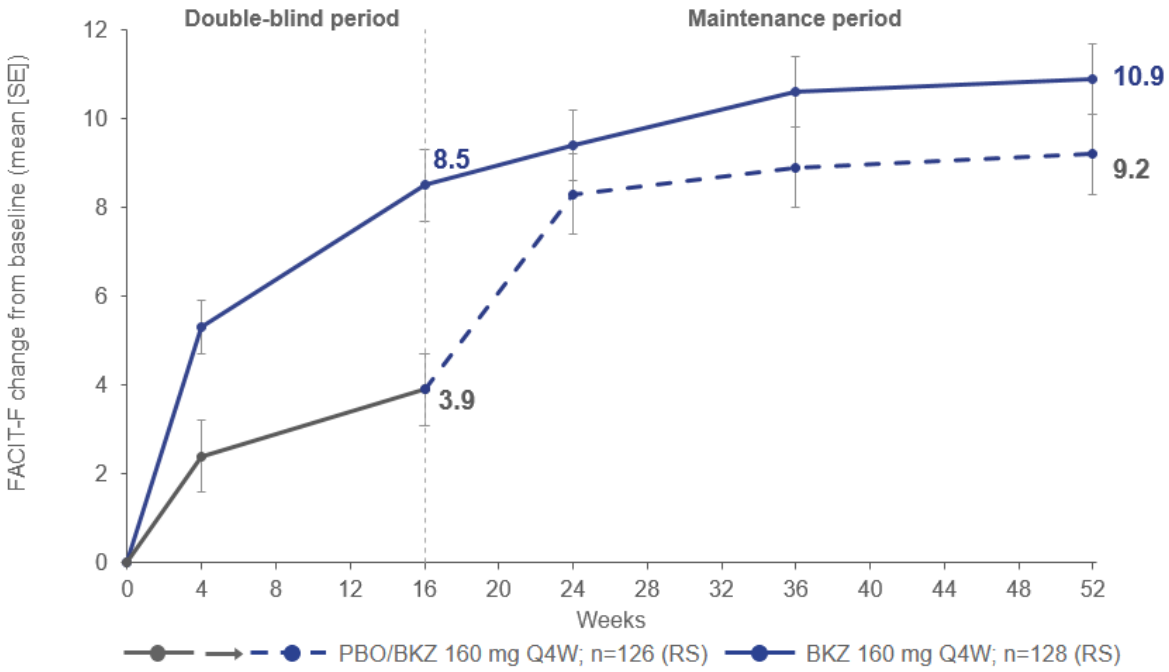
ASDAS-CRP CfB [MI], mean (SE)	BE MOBILE 1		BE MOBILE 2	
	Bimekizumab 160 mg Q4W N=128	Placebo N=126	Bimekizumab 160 mg Q4W N=221	Placebo N=111
Baseline	3.8 (0.2)	3.7 (0.1	3.7 (0.1)	3.7 (0.1)
Week 16	–1.5 (0.1)	–0.6 (0.1)	–1.4 (0.1)	–0.7 (0.1)
Week 52†	–1.8 (0.1)	–1.6 (0.1)	–1.7 (0.1)	–1.9 (0.1)

Source: Baraliakos, 2022 (145); Baraliakos, 2022 (144);
†Switch group, patients switched from placebo to bimekizumab at Week 16.
Abbreviations: ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score-C-reactive protein; CfB, change from baseline; MI, multiple imputation; Q4W, every 4 weeks; SE, standard error.

B.3.6.3.4 *FACIT-Fatigue*

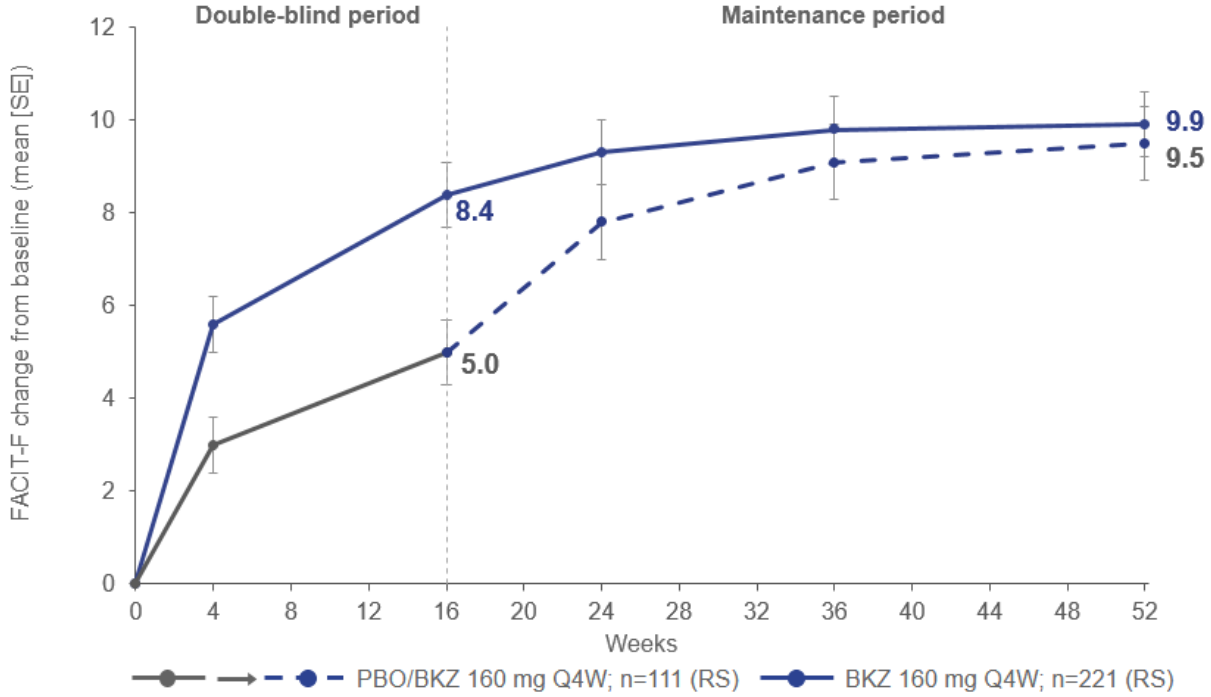
In BE MOBILE 1, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue subscale score mean CfB was higher (indicating an improvement) with bimekizumab (8.5) than placebo (3.9) at Week 16 (95% CI: 2.11, 6.21; p<0.001) (Figure 5). From Week 16 to Week 52, scores further increased with bimekizumab (10.9) and in patients who switched to bimekizumab (9.2). In BE MOBILE 2, FACIT-Fatigue score mean CfB was higher with bimekizumab (8.4) than placebo (5.0) at Week 16 (95% CI: 0.44, 4.04; p=0.015) (Figure 6). From Week 16 to Week 52, scores further increased with bimekizumab (9.9) and in patients who switched to bimekizumab (9.5).

Figure 5: BE MOBILE 1 FACIT-Fatigue scores to Week 52 (randomised set)



Source: UCB Data on file (150)
Abbreviations: BKZ, bimekizumab; CfB, change from baseline; FACIT, Functional Assessment of Chronic Illness Therapy; PBO, placebo., every 4 weeks.

Figure 6: BE MOBILE 1 FACIT-Fatigue scores to Week 52 (randomised set)



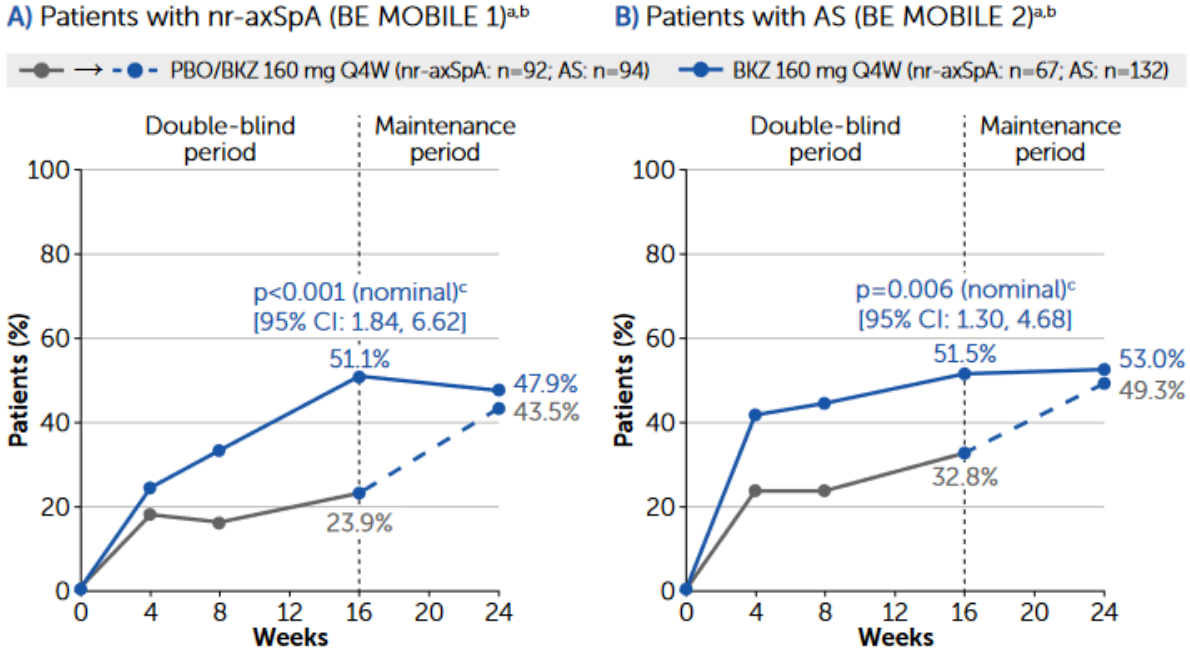
Source: UCB Data on file (151)
Abbreviations: BKZ, bimekizumab; CfB, change from baseline; FACIT, Functional Assessment of Chronic Illness Therapy; PBO, placebo., every 4 weeks.

B.3.6.3.5 *MASES index*

In BE MOBILE 1, in the patients with enthesitis at baseline (Maastrich Ankylosing Spondylitis Enthesitis Score [MASES] index score >0; bimekizumab group n=94, placebo group n=92), the bimekizumab 160 mg Q4W group had a higher proportion of patients reach an enthesitis-free state at Week 16 (based on the MASES index) compared with the placebo group (51.1% vs 23.9%, respectively; nominal p<0.001) (Figure 7).

In BE MOBILE 2, in the patients with enthesitis at baseline (MASES index score >0; bimekizumab group n=132, placebo group n=67), the bimekizumab 160 mg Q4W group had a higher proportion of patients reach an enthesitis-free state at Week 16 (based on the MASES index) compared with the placebo group (51.5% vs 32.8%, respectively; nominal p=0.006) (Figure 7).

Figure 7: Enthesitis-free state based on the MASES index at Week 16 (randomised set)



Source: Thaçi, 2022 Presented at EADV 2022 (152)
a MASES=0 in patients with baseline MASES >0; b Assessed in the subgroup of patients with enthesitis at baseline (MASES >0); c Nominal p values were not adjusted for multiplicity.
Abbreviations: AS, ankylosing spondylitis; BKZ, bimekizumab; CI, confidence interval; EADV, European Academy of Dermatology and Venereology; MASES, Maastricht Ankylosing Spondylitis Enthesitis; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; Q4W, every 4 weeks.

B.3.6.3.6 *SPARCC MRI*

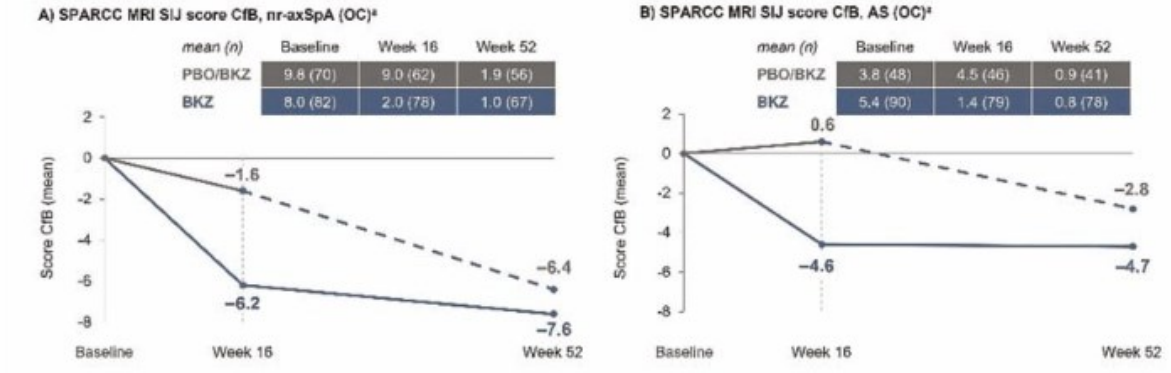
In BE MOBILE 1, the bimekizumab group had a greater mean reduction (indicating an improvement) from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) MRI score compared with placebo at Week 16 (–6.2 vs –1.6, respectively; 95% CI: –8.28, –3.16; p<0.001). The mean reduction in SPARCC MRI score further decreased at Week 52 (–7.6) with

bimekizumab. In patients who switched from placebo to bimekizumab at Week 16, mean SPARCC MRI score had also decreased at Week 52 (–6.4).

In BE MOBILE 2, the bimekizumab group had a greater mean reduction from baseline to Week 16 in SPARCC MRI score compared with placebo (which worsened) (–4.5 vs 0.6, respectively; (95% CI: –5.27, –2.03; p<0.001). The mean reduction in SPARCC MRI score further improved at Week 52 (–4.7) bimekizumab. In patients who switched from placebo to bimekizumab at Week 16, the mean reduction in SPARCC MRI score had also decreased at Week 52 (–2.8) (Figure 8).

Notably, in both BE MOBILE 1 and BE MOBILE 2, patients receiving bimekizumab 160 mg Q4W achieved disease remission (defined as a SPARCC MRI SIJ score of <2.0 (153)) at Week 16 (BE MOBILE 1 mean: 2.0; BE MOBILE 2 mean: 1.4) and Week 52 (BE MOBILE 1 mean: 1.0; BE MOBILE 2 mean: 0.8) (Figure 8).

Figure 8: SPARCC MRI SIJ score (randomised set)



Source: Baraliakos, 2022 (145).
Abbreviations: AS, ankylosing spondylitis; BKZ, bimekizumab; CfB, change from baseline; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axial spondyloarthritis; OC, observed case; PBO, placebo; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of Canada.

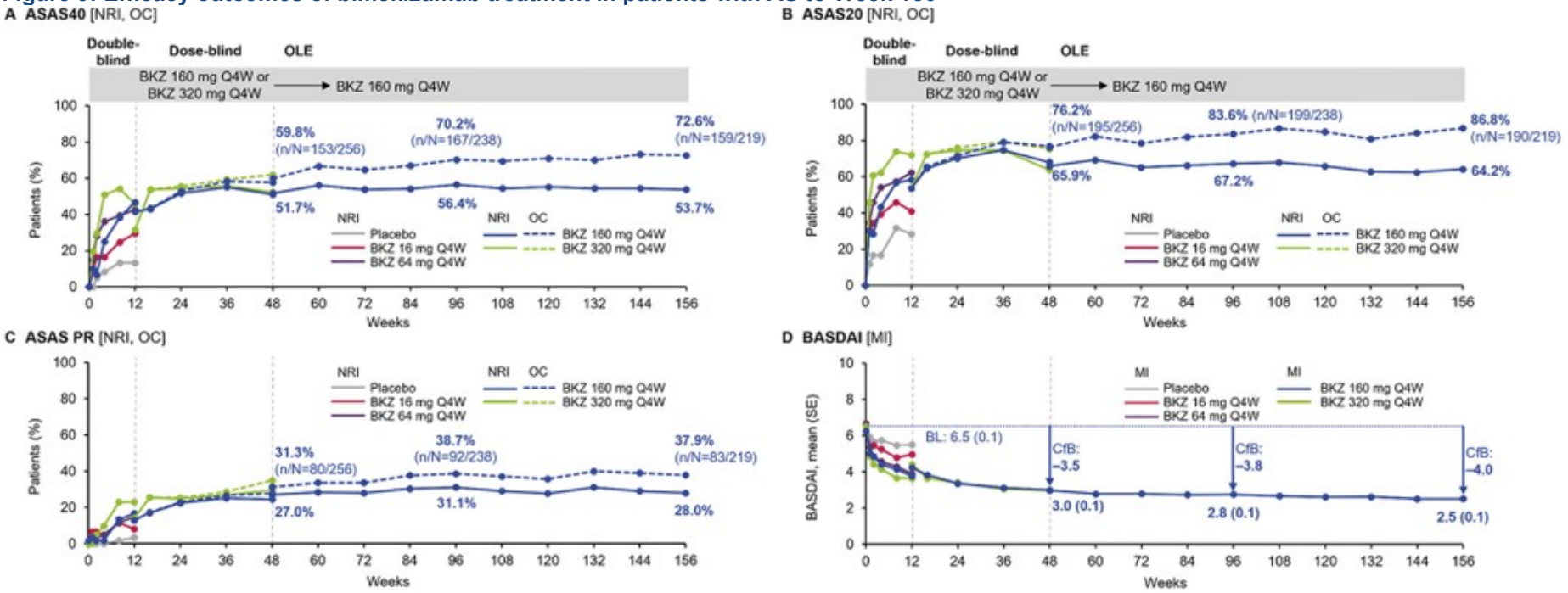
B.3.6.4 Supporting clinical effectiveness evidence (BE AGILE and BE AGILE 2)

Long-term clinical effectiveness evidence with bimekizumab in AS is available from the Phase 2b RCT (BE AGILE) and its open-label extension study (BE AGILE 2).

Patient disposition and baseline characteristics are reported in Appendix .

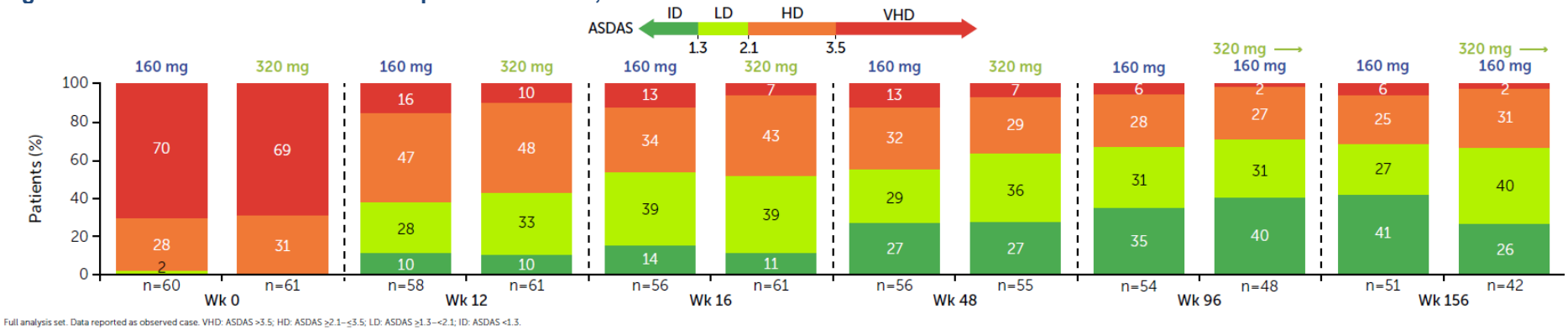
Efficacy outcomes (ASAS40, ASAS20, ASAS PR, and BASDAI) of bimekizumab treatment in patients with AS to week 156 are presented in Figure 9, ASDAS status is presented in Figure 10, with full outcomes reported in Appendix .

Figure 9: Efficacy outcomes of bimekizumab treatment in patients with AS to Week 156



Source: Baraliakos, 2022 (147)
Abbreviations: AS, ankylosing spondylitis; ASAS20, Assessment of SpondyloArthritis international Society20%; ASAS40, Assessment of SpondyloArthritis international Society 40%; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BKZ, bimekizumab; BL, baseline; CfB, change from baseline; MI, multiple imputation; NRI, non-responder imputation; OC, observed case; OLE, open-label extension; PR, partial remission; Q4W, every 4 weeks.

Figure 10 ASDAS states to week 156 in patients with AS, BE AGILE



Source: Navarro-Campan, 2022 (154)
Abbreviations: AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; HD, high disease; ID, inactive disease; LD, low disease; VHD, very high disease.

B.3.7 Subgroup analysis

Subgroup analyses of ASAS40 and ASDAS MI (Section B.3.7.1) by TNF-α inhibitor exposure at Week 16 using non-responder imputation (NRI) for randomised patients were pre-planned. Note, the sample size for study participants with prior TNF-α inhibitor exposure was small, and conclusions should be drawn with caution.

B.3.7.1 Subgroup analysis of ASAS40 and ASDAS MI by TNF-α inhibitor exposure

In patients with prior TNF-α inhibitor exposure, the ASAS40 response rate at Week 16 with bimekizumab was higher in BE MOBILE 1 and BE MOBILE 2 (60% and 40.5%, respectively) compared with placebo (11.8% and 17.6%, respectively). Results were similar in patients with no prior TNF-α inhibitor exposure, with ASAS40 response being higher with bimekizumab (46.6% and 45.7%, respectively) compared with placebo (22.9% and 23.4%, respectively)(47) (Table 20).

Table 20: Subgroup analysis of ASAS40 and ASDAS MI at Week 16 by TNF-α inhibitor exposure (OR 95% CI) in BE MOBILE 1 and BE MOBILE 2 (RS [NRI])

Endpoint	Study	N	TNF-α inhibitor exposure.	OR (95% CI)	Response % (BKZ/PBO)
ASAS40	BE MOBILE 1	27	Yes	10.69 (2.00, 6.16)	60.0/11.8
ASAS40		227	No	3.12 (1.73, 5.62)	46.6/22.9
ASAS40	BE MOBILE 2	54	Yes	3.48 (0.84, 14.40)	40.5/17.6
ASAS40		278	No	2.79 (1.59, 4.91)	45.7/23.4
ASDAS MI	BE MOBILE 1	27	Yes	5.86 (0.47, 72.81)	23.5/5.0
ASDAS MI		227	No	5.36 (2.23, 12.70)	24.8/5.8
ASDAS MI	BE MOBILE 2	54	Yes	2.35 (0.43, 12.77)	19.7/9.5
ASDAS MI		278	No	8.57 (2.96 24.75)	24.1/3.6

Source: UCB data on file (155); UCB data on file (156)
Abbreviations: ASAS40, Assessment of SpondyloArthritis international Society 40% response; ASDAS MI, Ankylosing Spondylitis Disease Activity Score major improvement; BKZ, bimekizumab; CI, confidence interval; NRI, non-responder imputation; OR, odds ratio; PBO, placebo; RS, randomised set; TNF-α, tumour necrosis factor alpha.

B.3.8 Meta-analysis

A pairwise meta-analysis was not considered applicable.

B.3.9 Indirect and mixed treatment comparisons

B.3.9.1 Nr-axSpA and AS NMA

No direct evidence comparing bimekizumab with the comparators defined in the final scope was identified in the SLR (Section B.3.1). Therefore, NMAs were conducted to evaluate the relative efficacy of bimekizumab vs approved treatments for separate populations of nr-axSpA and AS. For tolerability and safety, NMAs were conducted in a combined nr-axSpA and AS population. A feasibility assessment was conducted to assess whether studies identified by the SLR were suitable for inclusion in the NMA. The criteria for determining study inclusion/exclusion in the NMA is described in Appendix D. Ixekizumab is considered the most relevant comparator for bimekizumab as it is the most similar treatment, in terms of efficacy, tolerability and safety (Sections B.3.9.3 and B.3.9.5) and the most likely treatment to be displaced by bimekizumab in axSpA. Clinical experts expected that bimekizumab would be grouped alongside ixekizumab in UK clinical practice. Therefore, results against ixekizumab are presented in this document. Studies of unlicensed treatments or doses were excluded from the main NMA. However the scenario analysis presented in Section B.3.9.4 relaxes the inclusion criteria to include secukinumab doses with IV induction in the trials. Specifically, Section B.3.9.4 presents results vs secukinumab (150 mg and 300 mg, IV load and SC load) for ASAS40, BASDAI50, ASAS PR, and BASDAI CfB. Comparisons against all other treatments are presented in Appendix D.

B.3.9.2 NMA methods

A clinical SLR initiated in May 2012 was recently updated in April 2022 and January 2023, to identify RCT evidence assessing bimekizumab and relevant b/tsDMARDs for the treatment of patients with AS or nr-axSpA with an inadequate response to, intolerance of, or contraindication to NSAID therapy. NMA eligibility criteria were applied in a feasibility assessment to ensure that the trial data could be synthesised within a meta-analysis framework and studies were relevant to the decision problem.

Key efficacy outcomes presented in this submission are ASAS40, BASDAI50, ASAS PR, ASDAS MI, and BASDAI CfB, BASFI CfB, and fatigue numeric rating scale (NRS) CfB. Key tolerability and safety outcomes presented are discontinuation due to any reason, discontinuation due to AEs and SAEs. Detailed methods, eligibility criteria, and results of other outcomes evaluated are available in Appendix D. Outcomes were measured at 12–16 weeks, with preference given to 16-week data if studies reported measurements at more than one timepoint within this timeframe, and provided no treatment cross-over had occurred by the later time point, as this aligned with the follow-up timeframe for the primary and secondary endpoints in BE MOBILE 1 and 2.

Since b/tsDMARDs can be used at different stages in the treatment pathway, the efficacy analyses are assessed in the following populations:

- **b/tsDMARD naïve network:** Includes either studies where 100% of patients were b/tsDMARD-naïve, or studies reporting separate data for a b/tsDMARD-naïve subgroup
- **Predominantly b/tsDMARD-naïve network**: Includes studies where >50% of patients were b/tsDMARD-naïve, or it can be reasonably assumed that >50% of patients were b/tsDMARD-naïve
    - Across the trials included in the predominantly b/tsDMARD-naïve network, approximately 90% of patients were b/tsDMARD-naïve (67–100% in nr-axSpA and 61–100% in AS).
- **b/tsDMARD-experienced network:** Includes studies where 100% of patients were b/tsDMARD-experienced, or studies reporting separate data for a b/tsDMARD-experienced subgroup. Of note, this network was only possible for the AS population.

The predominantly b/tsDMARD-naïve network provided the most robust and complete set of efficacy results and is therefore presented in the submission for both nr-axSpA and AS, with the b/tsDMARD-experienced networks also presented here for AS (the b/tsDMARD-naïve networks are presented in Appendix D).

Scenario analyses were conducted for AS to estimate the efficacy of secukinumab Q4W SC at a maintenance dose of 300 mg using data from the MEASURE 1 and MEASURE 3 secukinumab trials. These trials were not included in the main NMA because the initial loading phase for these two trials included an IV loading stage. Whilst secukinumab 300 mg Q4W (SC load) is used in clinical practice European Medicines Agency/European Public Affairs Committee (EMA/EPAC), approval does not extend to IV loading. Furthermore the initial IV loading may not be equivalent to SC loading (150 mg by SC injection with initial dosing at Weeks 0, 1, 2, 3 and 4). This analysis is therefore intended to provide an approximation of the efficacy of 300 mg Q4W SC. The impact of IV loading versus SC loading can be approximated by comparing secukinumab 150 mg Q4W SC (IV load) with secukinumab 150 mg Q4W SC (SC load) using MEASURE 1 and MEASURE 3 data. A comparison of 150 mg Q4W SC (IV load) with 300 mg Q4W SC (IV load) could be used to approximate the impact of increasing dose from 150 mg to 300 mg using MEASURE 3 data.

Due to limited reporting of outcomes by prior b/tsDMARD therapy in key tolerability and safety outcomes, the safety analyses are presented in the overall population irrespective of prior b/tsDMARD. The AS and nr-axSpA networks were combined for the safety analyses to increase the number of events and decrease uncertainty. Combining populations for tolerability and safety

outcomes was considered appropriate because indication and previous TNF-α inhibitor exposure were not expected to impact these outcomes.

The Bayesian NMA was conducted in WinBUGs (157) using validated code available from NICE Decision Support Unit (DSU) and standard methods for evidence synthesis (158-161). A binomial model with logit link was used for binomial outcomes, and a normal model with identity link was used for continuous outcomes. Placebo-adjusted models included the log odds of response or change from baseline in placebo arm as an interaction term. The WinBUGs models were run for a minimum burn-in of 10,000 iterations to maximise convergence. Subsequently, three chains of a minimum 1,000 samples (3,000 simulations) were drawn from the posterior distributions.

For each NMA, the models considered were fixed effects, random effects, fixed effects with placebo adjustment and random effects with placebo adjustment models. The appropriateness of placebo adjustment was assessed using bubble plots. Each model was assessed for fit using modified deviance information criterion. Where placebo adjustment was not feasible, where the deviance information criterion (DIC) showed little difference, or where random effects produced implausible credible intervals (CrI), fixed effects models were preferred.

The most suitable models in the efficacy NMAs were deemed to be fixed-effects placebo-adjusted for most of the AS NMAs with fixed-effect analysis for the b/tsDMARD-experienced network and for nr-axSpA. This was because:

- The DIC fit statistic did not differentiate between fixed and random effect models, since the DICs were within ±5.
- Fixed-effect models provided the most reliable results compared with the random-effects models, which tended to produce unrealistically large 95% CrIs for most outcomes; likely due to the small number of studies available for each comparison so that the between study variance could not be estimated with accuracy.
- For the binomial outcomes (ASAS40, BASDAI50, ASAS PR, ASDAS-MI, and continuous outcomes (BASDAI, BASFI, fatigue NRS), there was a trend indicating an inverse-relationship between placebo response and the treatment effect; that is, higher odds of a response or larger change from baseline in the placebo arm which may lead to a lower estimate for the comparative OR or mean difference (MD).

Given the above, the intension was to use fixed effect placebo-adjusted analysis where feasible. However unadjusted fixed effects was appropriate for most of the b/tsDMARD-experienced network analysis and for nr-axSpA due to a smaller network and fewer patients.

For the tolerability and safety outcomes in the combined nr-axSpA and AS population, unadjusted fixed-effect models were also preferred.

The model presented in the scenario analysis was kept consistent across the outcomes to isolate the impact of the different secukinumab loading approaches. For the naïve networks, the model presented is fixed effects placebo-adjusted since this model is preferred for most outcomes. For the bDMARD-experienced network, the model presented is fixed effects without adjustment.

Assessment of consistency between direct and indirect treatment effects in a network is only possible if there are loops of evidence formed from separate, independent trials to inform the direct and indirect estimates. One such loop was identified in the current networks in the predominantly b/tsDMARD-naïve AS network. An informal assessment was conducted to assess whether the direct estimate of ADA vs IXE from COAST-V (which had an ADA and PBO control arm) was potentially inconsistent with the indirect estimate of ADA vs IXE from the NMA. This was done by reviewing the ADA vs PBO and IXE vs PBO study level estimates (see the study-level forest plots Appendix D). These forest plots did not indicate any major heterogeneity in the study-level estimates and so it is reasonable to assume that the BKZ comparisons are not impacted by any inconsistency arising from the COAST-V ADA vs PBO estimates.

B.3.9.3 NMA efficacy results

In total, 341 publications reporting on 65 unique trials were included in the SLR; the feasibility assessment determined that 37 of these trials were suitable for inclusion in the NMA, comprising 9 trials in nr-axSpA, 27 in AS, and one that reported separate data for the two populations (RAPID-axSpA). Reasons for exclusion of the 28 remaining trials are provided in Appendix D. In general, the trials were similar in terms of their main baseline characteristics (where reported). Forest plots for direct comparisons are provided in Appendix D as a means of assessing heterogeneity.

For this assessment, only results compared with ixekizumab 80 mg Q4W are presented here, as this was the most relevant comparator for this submission. For nr-axSpA, the analyses presented here are ASAS40, BASDAI, BASDAI50, BASFI, and fatigue NRS for the predominantly b/tsDMARD-naïve network. No ixekizumab data for ASAS PR and ASDAS MI were identified for the nr-axSpA population.

The following outcomes are presented here for AS: ASAS40, ASAS PR, ASDAS MI, BASDAI50, BASDAI, BASFI, and fatigue NRS, for the predominantly b/tsDMARD-naïve and the b/tsDMARD-experienced networks.

Forest plots of the results for bimekizumab vs other comparators of interest included in the NMA are available in the appendix for the following outcomes (where feasible): ASAS20, ASAS40, ASAS 5/6, ASAS PR, ASDAS<2.1, ASDAS- CII, ASDAS ID, ASDAS MI, BASDAI50, ASDAS-

CRP, ASQoL, BASDAI, BASFI, BASMI, fatigue NRS, MASES, NSP, PtGADA, SF-36 MCS and PCS.

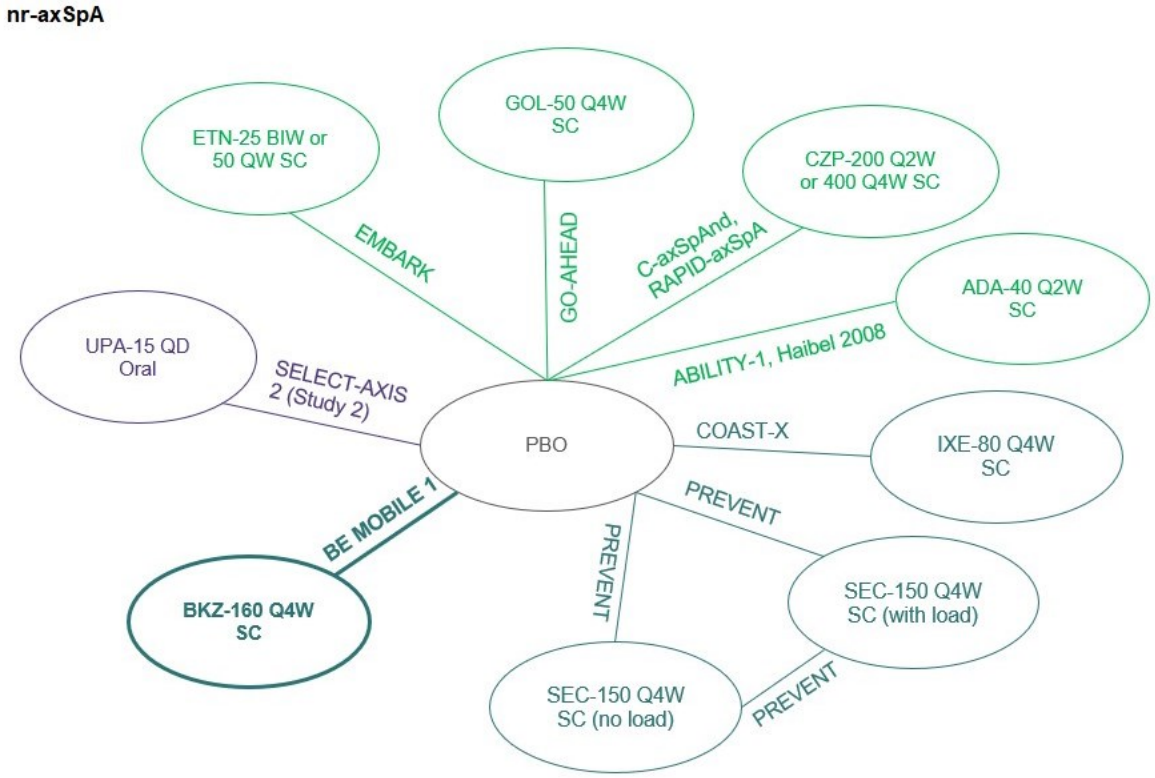
All other available analyses can be found in the corresponding NMA reports for nr-axSpA and AS (162, 163).

B.3.9.3.1 *Nr-axSpA*

B.3.9.3.1.1 Overview of included studies

In total, 10 studies (2,428 patients) were included in the nr-axSpA NMA (included studies and the network diagram are provided in Table 21 and Figure 11, respectively). Overall, evaluated trials had a low risk of bias; no studies were deemed unsuitable for inclusion in the NMA based on concerns regarding risk of bias. Note that it was not possible to perform NMA analyses of ASAS PR or ASDAS MI for ixekizumab due to lack of data in the COAST-X trial (164).

Figure 11: General network diagram for predominantly b/tsDMARD-naïve network in nr-axSpA (N = 10)†



†Study population is inadequate response to ≥1 NSAID and studies include 66% to 100% bDMARD-naïve patients (approximately 90% of included patients were bDMARD-naïve)
Abbreviations: ADA, adalimumab; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; BKZ, bimekizumab; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; BIW, twice a week; IXE, ixekizumab; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; QD, every day; QW, every week; SC, subcutaneous; SEC, secukinumab; UPA, upadacitinib.

Table 21: List of studies included in the nr-axSpA NMA (N=10)

Study	Drug class	Intervention	Population	% Naïve	Predominantly b/tsDMARD-naïve						
					ASAS40	ASAS PR	ASDAS MI	BASDAI50	BASDAI	BASFI	Fatigue NRS
BE MOBILE 1 (141)	IL-17A/F inhibitor	Bimekizumab 160 mg Q4W SC	Predominantly b/tsDMARD-naïve	89	✓	✓	✓	✓	✓	✓	✓
COAST-X (164)	IL-17A inhibitor	Ixekizumab 80 mg Q4W SC	b/tsDMARD naïve	100	✓	×	×	✓	✓	✓	✓
PREVENT (165)		Secukinumab 150 mg Q4W SC (with loading and no loading[†])	Predominantly b/tsDMARD-naïve	90	✓	✓	×	✓	×	×	×
SELECT-AXIS 2 (Study 2) (166)	JAK inhibitor	Upadacitinib 15 mg QD oral	Predominantly b/tsDMARD-naïve	67	✓	✓	✓	✓	×	✓	✓
ABILITY-1 (167)	TNF-α inhibitor	Adalimumab 40 mg Q2W SC	b/tsDMARD naïve	100	✓	✓	✓	✓	✓	✓	×
Haibel 2008 (168)		Adalimumab 40 mg Q2W SC	Predominantly naïve	Unknown	✓	✓	×	×	✓	✓	×
C-axSpAnd (169)		Certolizumab pegol 200 mg Q2W SC[‡]	Predominantly b/tsDMARD-naïve	94	✓	✓	✓	✓	✓	✓	✓

Study	Drug class	Intervention	Population	% Naïve	Predominantly b/tsDMARD-naïve						
					ASAS40	ASAS PR	ASDAS MI	BASDAI50	BASDAI	BASFI	Fatigue NRS
RAPID-axSpA (38)		Certolizumab pegol 200 mg Q2W or 400 mg Q4W SC‡	Predominantly b/tsDMARD-naïve	89	✓	✓	✓	✓	✓	✓	✓
EMBARK (170)		Etanercept 50 mg QW SC	b/tsDMARD naïve	100	✓	✓	×	✓	✓	✓	×
GO-AHEAD (171)		Golimumab 50 mg Q4W SC	b/tsDMARD naïve	100	✓	✓	×	✓	✓	✓	×

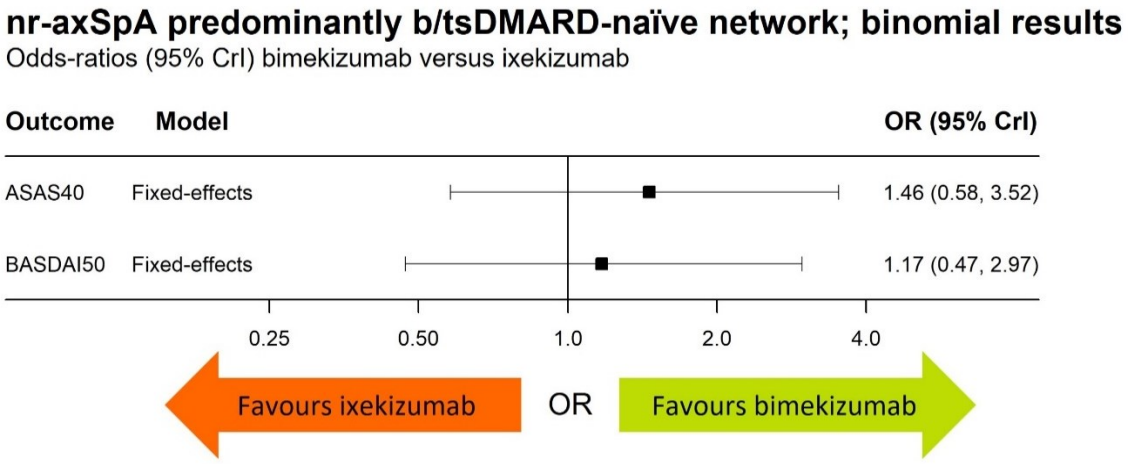
†Refers to secukinumab with or without an initial 150 mg QW loading dose at Weeks 0, 1, 2, 3 and 4. ‡ Certolizumab pegol 200 mg Q2W and certolizumab pegol 400 mg Q4W SC pooled in the NMA on the assumption that these treatments are equivalent

Abbreviations: ASAS40, Assessment of SpondyloArthritis international Society 40% improvement; ASAS PR, Assessment of SpondyloArthritis international Society partial remission; ASDAS MI, Ankylosing Spondylitis Disease Activity Score major improvement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50, 50% improvement); BASFI, Bath Ankylosing Spondylitis Functional Index; b/tsDMARD, biological/targeted synthetic disease modifying anti-rheumatic drug; IL, interleukin; JAK, Janus kinase; NMA, network meta-analysis; nr-axSpA, non-radiographic axial spondyloarthritis; NRS, numeric rating scale; Q2W, every 2 weeks; Q4W, every four weeks; QD, every day; QW, very week; SC, subcutaneous.

B.3.9.3.1.2 Predominantly (>50%) b/tsDMARD-naïve network results

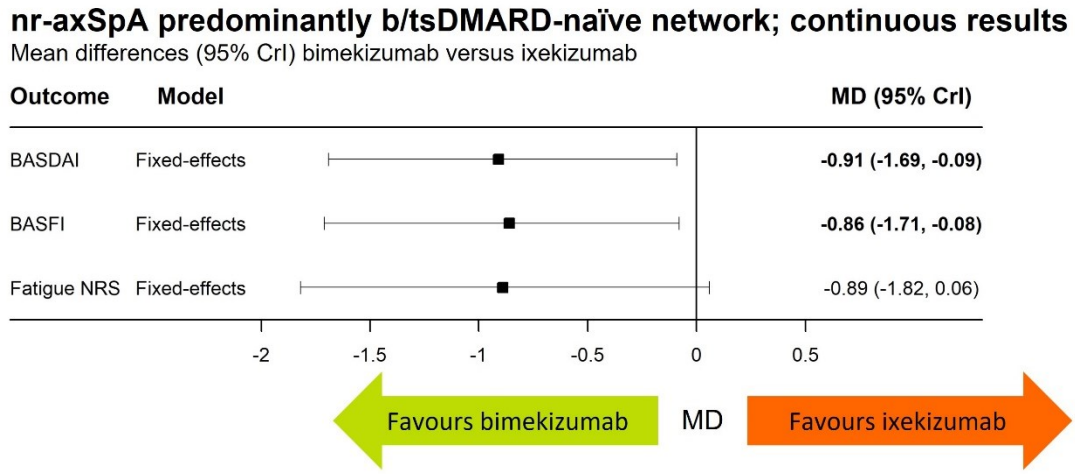
Results for the predominantly b/tsDMARD-naïve network of bimekizumab vs ixekizumab in nr-axSpA are summarised in Figure 12 (binomial outcomes) and Figure 13 (continuous outcomes), respectively. Bimekizumab was associated with significantly improved change from baseline BASDAI and BASFI vs ixekizumab in predominantly b/tsDMARD-naïve patients with nr-axSpA. No significant differences were observed between bimekizumab and ixekizumab for ASAS40, BASDAI50, and fatigue NRS. Comparisons vs other treatments in the NMA network across all outcomes are provided in Appendix D.

Figure 12: Forest plot of bimekizumab vs ixekizumab in predominantly b/tsDMARD-naïve patients with nr-axSpA: ASAS40 and BASDAI50 (binomial outcomes, OR 95% CrI)



Abbreviations: ASAS40, Assessment of SpondyloArthritis international Society 40% response; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50% response; CrI, credible interval; nr-axSpA, non-radiographic axial spondyloarthritis; OR, odds ratio.

Figure 13: Forest plot of bimekizumab vs ixekizumab in predominantly b/tsDMARD-naïve patients with nr-axSpA: BASDAI, BASFI, fatigue NRS (continuous outcomes, MD 95% CrI)



Abbreviations: b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CrI, credible interval; MD, mean difference; nr-axSpA, non-radiographic axial spondyloarthritis; NRS, numeric rating scale.

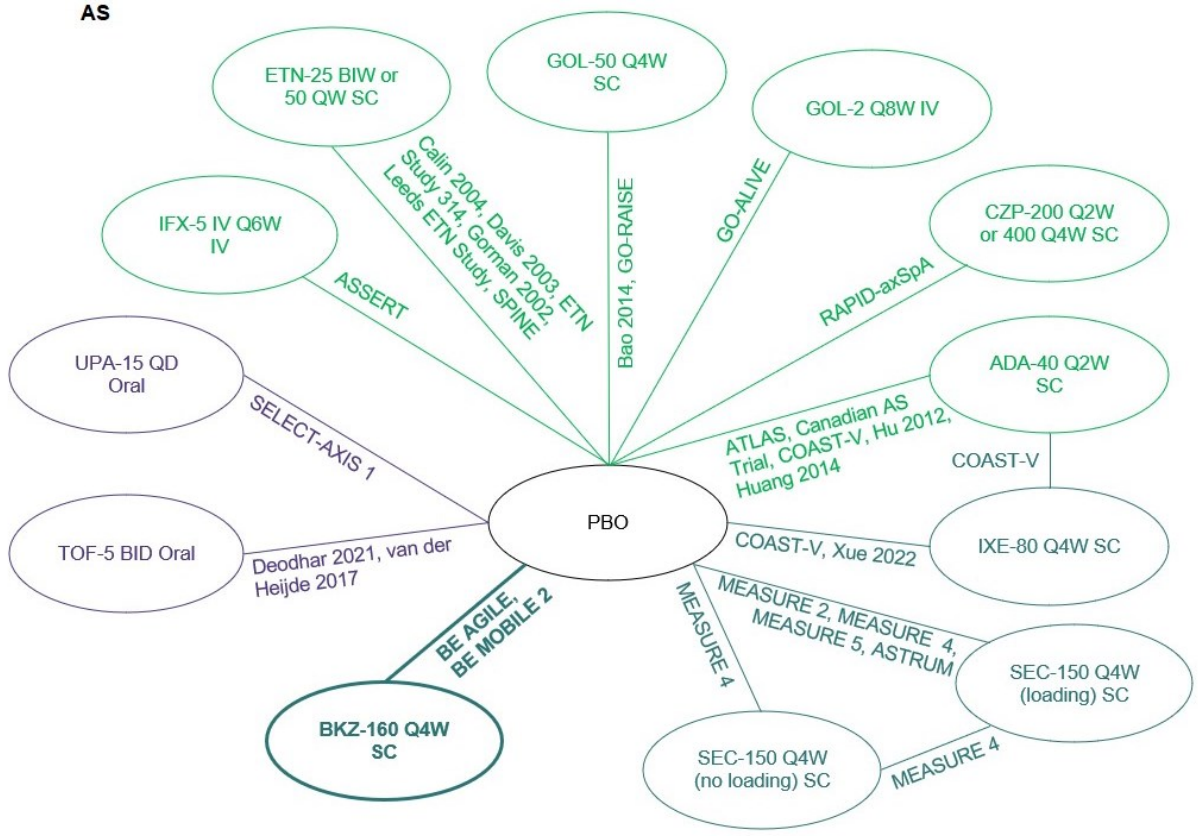
B.3.9.3.2 *AS*

B.3.9.3.2.1 Overview of included studies

In total, 28 studies were included in the AS NMAs across the three networks. There were 26 studies (5,271 patients) in the predominantly b/tsDMARD-naïve network (included studies and the network diagram are provided in Table 22 and Figure 14, respectively). The b/tsDMARD-experienced network included 9 studies (1,048 patients) (Table 22 and Figure 15). Overall, evaluated trials had a low risk of bias; no studies were deemed unsuitable for inclusion in the NMA based on concerns regarding risk of bias.

Note that it was not possible to perform NMA analyses of ASAS PR compared to ixekizumab in the b/tsDMARD-experienced network due to lack of data. Moreover, some studies reported zero events in the PBO group for outcomes in this b/tsDMARD-experienced population. This caused convergence issues for some contrasts. Given the small subgroups and limited dataset, model alternatives, e.g. more informative priors, were not explored.

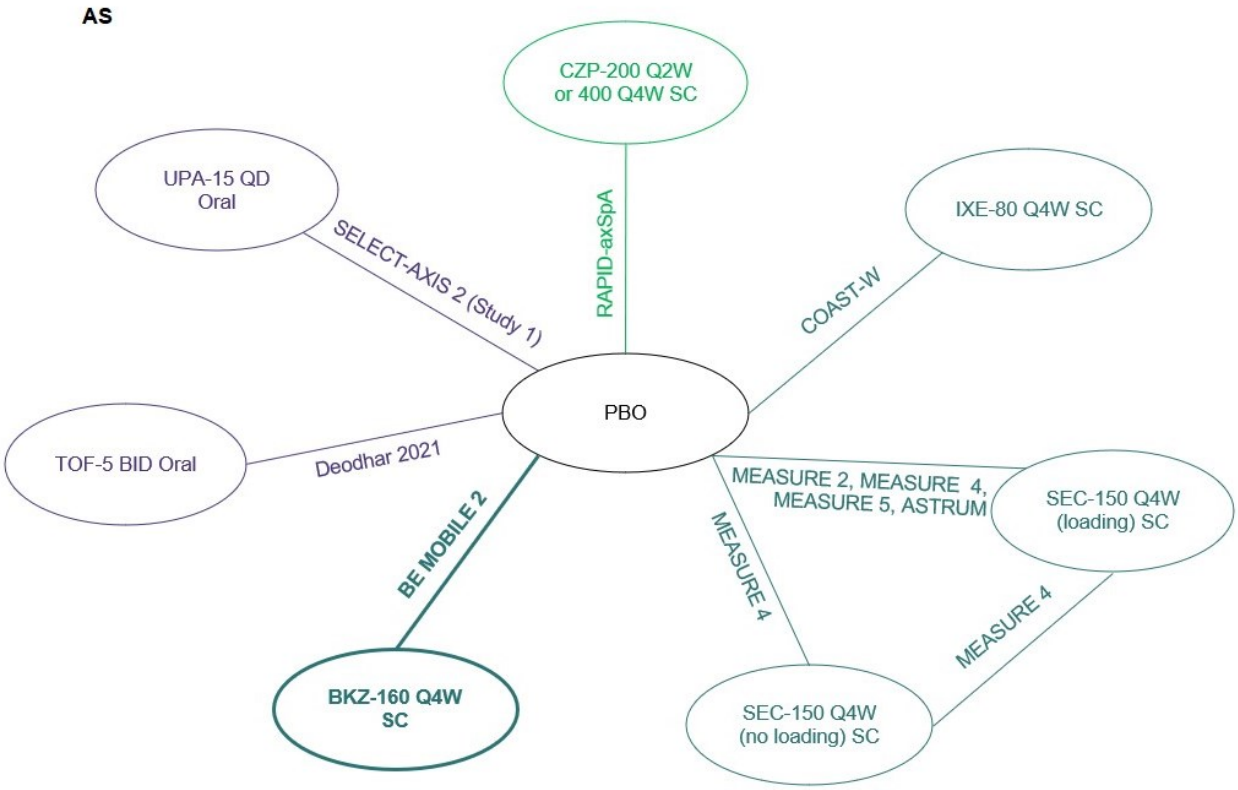
Figure 14: General network diagram for predominantly b/tsDMARD-naïve network evidence in AS (N = 26)†



†Study population is inadequate response to ≥1 NSAID studies and 61%-100% bDMARD-naïve patients. Approximately 90% of subjects included in this network were bDMARD-naïve
Abbreviations: ADA, adalimumab; AS, ankylosing spondylitis; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; BIW, twice a week; BKZ, bimekizumab; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; IV, intravenous; IXE, ixekizumab; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks;

Q6W, every 6 weeks; Q8W, every 8 weeks; QD, every day; QW, every week; SC, subcutaneous; SEC, secukinumab; TOF, tofacitinib; UPA, upadacitinib.

Figure 15: Network diagram for b/tsDMARD-experienced network evidence in AS (N = 9)†



†Study population is inadequate response to ≥1 NSAID and either 100% bDMARD-experienced patients or data available for the subset of patients that have had 1 or more prior bDMARD (>9 patients).
Abbreviations: BID, twice a day; BKZ, bimekizumab; CZP, certolizumab pegol; IXE, ixekizumab; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; QD, every day; SC, subcutaneous; SEC, secukinumab; UPA, upadacitinib.

Table 22: List of studies included in the AS NMA

Study	Drug class	Intervention	Population	% Naive	Predominantly b/tsDMARD-naïve							b/tsDMARD-experienced						
					ASAS40	ASAS PR	ASDAS MI	BASDAI50	BASDAI	BASFI	Fatigue NRS	ASAS40	ASAS PR	ASDAS MI	BASDAI50	BASDAI	BASFI	Fatigue NRS
BE AGILE (172)	IL-17A/F inhibitor	Bimekizumab 160 mg Q4W SC	Predominantly b/tsDMARD-naïve	89	✓	✓	✓	✓	✓	✓	✓	NA	NA	NA	NA	NA	NA	NA
BE MOBILE 2 (142, 173)		Bimekizumab 160 mg Q4W SC	Predominantly b/tsDMARD-naïve	82	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
COAST-V (174)	IL-17A inhibitor	Ixekizumab 80 mg Q4W SC	b/tsDMARD naïve	100	✓	✓	✓	✓	✓	✓	✓	NA	NA	NA	NA	NA	NA	NA
COAST-W (175)		Ixekizumab 80 mg Q4W SC	b/tsDMARD-experienced	0	NA	NA	NA	NA	NA	NA	NA	✓	✓	✓	✓	✓	✓	✓
Xue 2022 (176)		Ixekizumab 80 mg Q4W SC	b/tsDMARD-experienced	88	✓	×	×	×	✓	✓	×	NA	NA	NA	NA	NA	NA	NA
MEASURE 2 (62)		Secukinumab 150 mg Q4W (SC loading)†	Predominantly b/tsDMARD-naïve	61	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	×	✓
MEASURE 4 (177)		Secukinumab 150 mg Q4W (SC loading/no loading)†	Predominantly b/tsDMARD-naïve	72	✓	×	×	×	✓	×	×	✓	×	×	×	✓	×	×
MEASURE 5 (178)		Secukinumab 150 mg Q4W (SC loading)†	Predominantly b/tsDMARD-naïve	79	✓	✓	×	×	✓	×	×	✓	✓	×	×	✓	×	×
ASTRUM (179)		Secukinumab 150 mg Q4W (SC loading)†	Predominantly b/tsDMARD-naïve	71	✓	✓	×	✓	✓	×	×	✓	×	×	×	×	×	×
Deodhar 2021 (112)	JAK inhibitor	Tofacitinib 5 mg BID oral	Predominantly b/tsDMARD-naïve	76	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	×

Study	Drug class	Intervention	Population	% Naive	Predominantly b/tsDMARD-naïve							b/tsDMARD-experienced						
					ASAS40	ASAS PR	ASDAS MI	BASDAI50	BASDAI	BASFI	Fatigue NRS	ASAS40	ASAS PR	ASDAS MI	BASDAI50	BASDAI	BASFI	Fatigue NRS
van der Heijde 2017 (180)		Tofacitinib 5 mg BID oral	b/tsDMARD naïve	100	✓	✓	✓	✓	✓	✓	×	NA	NA	NA	NA	NA	NA	NA
SELECT-AXIS 1 (181)		Upadacitinib 15 mg QD oral	b/tsDMARD naïve	100	✓	✓	✓	✓	×	✓	✓	NA	NA	NA	NA	NA	NA	NA
SELECT-AXIS 2 (Study 1) (182)		Upadacitinib 15 mg QD oral	b/tsDMARD-experienced	0	NA	NA	NA	NA	NA	NA	NA	✓	✓	×	✓	✓	✓	✓
ATLAS (183)	TNF-α inhibitor	Adalimumab 40 mg Q2W SC	b/tsDMARD naïve	100	✓	✓	✓	✓	✓	✓	✓	NA	NA	NA	NA	NA	NA	NA
Canadian AS Trial (184)		Adalimumab 40 mg Q2W SC	b/tsDMARD naïve	100	×	×	×	×	✓	✓	×	NA	NA	NA	NA	NA	NA	NA
COAST-V (174)		Adalimumab 40 mg Q2W SC	b/tsDMARD naïve	100	✓	✓	✓	✓	✓	✓	✓	NA	NA	NA	NA	NA	NA	NA
Hu 2012 (185)		Adalimumab 40 mg Q2W SC	b/tsDMARD naïve	100	×	×	×	×	✓	✓	×	NA	NA	NA	NA	NA	NA	NA
Huang 2014 (186)		Adalimumab 40 mg Q2W SC	b/tsDMARD naïve	100	✓	✓	✓	✓	✓	✓	✓	NA	NA	NA	NA	NA	NA	NA
RAPID-axSpA (38)		Certolizumab pegol 200 mg Q2W or 400 mg Q4W SC	Predominantly b/tsDMARD-naïve	85	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Calin 2004 (187)		Etanercept 25 mg BIW SC	b/tsDMARD naïve	100	×	×	×	×	✓	✓	✓	NA	NA	NA	NA	NA	NA	NA
Davis 2003 (188)		Etanercept 25 mg BIW SC	b/tsDMARD naïve	100	✓	×	×	×	×	×	×	NA	NA	NA	NA	NA	NA	NA
ETN Study 314 (189)		Etanercept 50 mg QW SC or 25 mg BIW SC	b/tsDMARD naïve	100	✓	✓	×	✓	✓	✓	✓	NA	NA	NA	NA	NA	NA	NA

Study	Drug class	Intervention	Population	% Naive	Predominantly b/tsDMARD-naïve							b/tsDMARD-experienced						
					ASAS40	ASAS PR	ASDAS MI	BASDAI50	BASDAI	BASFI	Fatigue NRS	ASAS40	ASAS PR	ASDAS MI	BASDAI50	BASDAI	BASFI	Fatigue NRS
Gorman 2002 (190)		Etanercept 25 mg BIW SC	b/tsDMARD naïve	100	×	×	×	×	×	✓	×	NA	NA	NA	NA	NA	NA	NA
Leeds ETN Study (191)		Etanercept 25 mg BIW SC	b/tsDMARD naïve	100	✓	×	×	✓	✓	✓	×	NA	NA	NA	NA	NA	NA	NA
SPINE (192)		Etanercept 50 mg QW SC	b/tsDMARD naïve	100	✓	✓	✓	✓	✓	✓	×	NA	NA	NA	NA	NA	NA	NA
GO-ALIVE (193)		Golimumab 2 mg/kg Q8W IV	Predominantly b/tsDMARD-naïve	85	✓	✓	✓	✓	✓	✓	×	NA	NA	NA	NA	NA	NA	NA
Bao 2014 (194)		Golimumab 50 mg Q4W SC	b/tsDMARD naïve	100	✓	✓	×	✓	×	✓	×	NA	NA	NA	NA	NA	NA	NA
GO-RAISE (195)		Golimumab 50 mg Q4W SC	b/tsDMARD naïve	100	✓	✓	✓	✓	✓	✓	×	NA	NA	NA	NA	NA	NA	NA
ASSERT‡ (196)		Infliximab 5 mg Q6W IV	Predominantly b/tsDMARD-naïve	Unknown	✓	×	×	×	×	×	×	NA	NA	NA	NA	NA	NA	NA

†Refers to secukinumab with or without an initial 150 mg QW loading dose at Weeks 0, 1, 2, 3 and 4; ‡Unknown % of bDMARD-naïve patients, but reasonable to assume >50% patients were bDMARD-naïve.

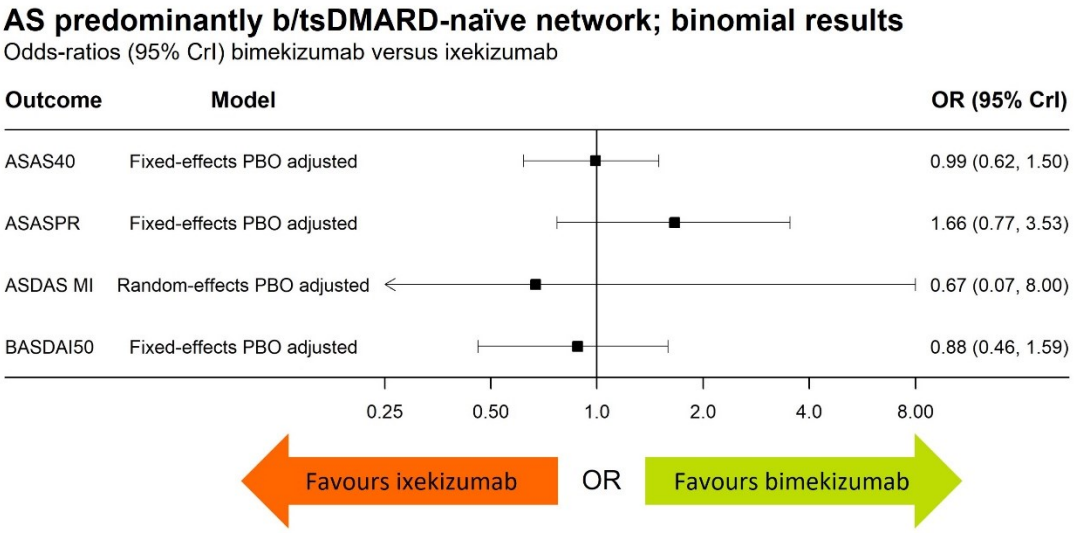
Abbreviations: AS, ankylosing spondylitis; ASAS40, Assessment of SpondyloArthritis international Society 40% response; ASASPR, Assessment of SpondyloArthritis international Society PR, partial remission; ASDAS MI, Ankylosing Spondylitis Disease Activity Score major improvement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50% response; BASFI, Bath Ankylosing Spondylitis Functional Index; b/tsDMARD, biological/targeted synthetic disease modifying anti-rheumatic drug; BID, twice daily; BIW, twice weekly; IL, interleukin; IV, intravenous; JAK, Janus kinase; NA, not applicable; NMA, network meta-analysis; NRS, numeric rating scale; Q2W, every 2 weeks; Q4W, every four weeks; QD, every day; QW, very week; SC, subcutaneous.

B.3.9.3.2.2 Predominantly (>50%) b/tsDMARD-naïve network results

Results for the predominantly b/tsDMARD-naïve network of bimekizumab vs ixekizumab in AS are summarised in Figure 16 (binomial outcomes) and Figure 17 (continuous outcomes). Bimekizumab was associated with similar ASAS40, ASAS PR, ASDAS MI, BASDAI50, BASDAI, BASFI, and fatigue NRS outcomes vs ixekizumab in predominantly b/tsDMARD-naïve patients with AS.

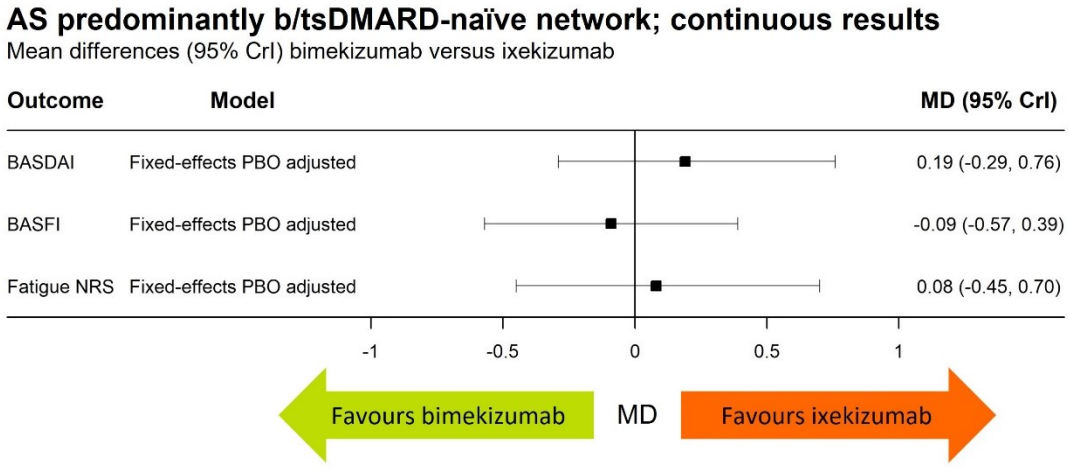
Comparisons vs other treatments in the NMA network across all outcomes are provided in Appendix D.

Figure 16: Forest plot of bimekizumab vs ixekizumab in predominantly b/tsDMARD-naïve patients with AS: ASAS40, ASAS PR, BASDAI50, ASDAS MI (binomial outcomes, OR 95% CrI)



Abbreviations: AS, ankylosing spondylitis; ASAS PR, Assessment of SpondyloArthritis international Society Partial Remission; ASAS40, Assessment of SpondyloArthritis international Society 40% response; ASDAS MI, Ankylosing Spondylitis Disease Activity Score major improvement; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50% response; CrI, credible interval; OR, odds ratio.

Figure 17: Forest plot of bimekizumab vs ixekizumab in predominantly b/tsDMARD-naïve patients with AS: BASDAI, BASFI, fatigue NRS (continuous outcomes, MD 95% CrI)



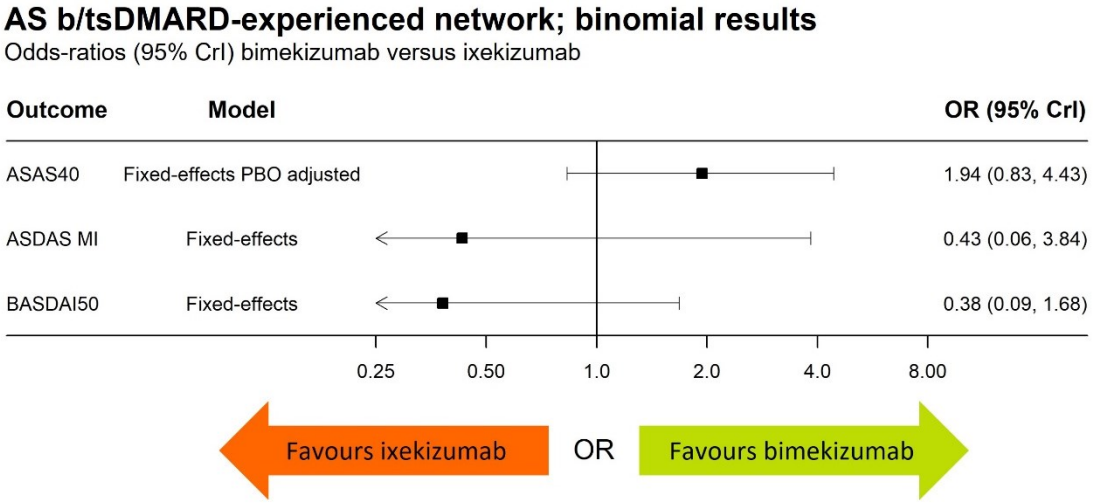
Abbreviations: AS, ankylosing spondylitis; ASAS40, Assessment of SpondyloArthritis international Society 40% response; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50% response; CrI, credible interval; MD, mean difference.

B.3.9.3.2.3 b/tsDMARD experienced network results

Results for the b/tsDMARD-experience network of bimekizumab vs ixekizumab in AS are summarised in Figure 18 (binomial outcomes) and Figure 19 (continuous outcomes). Bimekizumab was associated with similar ASAS40, ASDAS MI, BASDAI50, BASDAI, BASFI, and fatigue NRS outcomes vs ixekizumab in predominantly b/tsDMARD-naïve patients with AS. It was not possible to assess ASAS PR given the small subgroups and limited dataset.

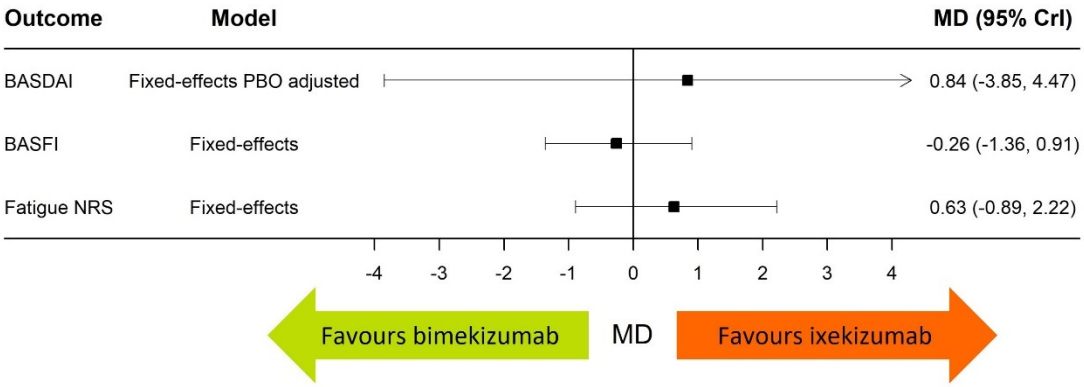
Comparisons vs other treatments in the NMA network across all outcomes are provided in Appendix D.

Figure 18: Forest plot of bimekizumab vs ixekizumab in b/tsDMARD-experienced patients with AS: ASAS40, BASDAI50, ASDAS MI, (binomial outcomes, OR 95% CrI)



Abbreviations: AS, ankylosing spondylitis; ASAS PR, Assessment of SpondyloArthritis international Society Partial Remission; ASAS40, Assessment of SpondyloArthritis international Society 40% response; ASDAS MI, Ankylosing Spondylitis Disease Activity Score major improvement; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50% response; CrI, credible interval; OR, odds ratio.

Figure 19: Forest plot of bimekizumab vs ixekizumab in b/tsDMARD-experienced patients with AS: BASDAI, BASFI, fatigue NRS (continuous outcomes, MD 95% CrI)



Abbreviations: AS, ankylosing spondylitis; ASAS40, Assessment of SpondyloArthritis international Society 40% response; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50% response; CrI, credible interval; MD, mean difference.

B.3.9.4 Scenario analysis

Scenario analyses for bimekizumab versus IL-17A inhibitors comparators are presented in this section. The IL-17A inhibitors comparators presented in the scenario analyses (subject to data availability) are:

- Ixekizumab 80 mg Q4W SC
- Secukinumab 150 mg Q4W (SC load)

- Secukinumab 150 mg Q4W (SC no load)
- Secukinumab 150 mg Q4W (IV load)
- Secukinumab 300 mg Q4W (IV load).

Key efficacy outcomes presented in the scenario analysis are ASAS40, BASDAI50, ASAS PR, and BASDAI CfB. Where there is no data for secukinumab 300 mg Q4W (IV load) and secukinumab 150 mg Q4W (IV load), results for bimekizumab versus the remaining IL-17A inhibitor comparators are presented, using the main NMA networks.

B.3.9.4.1 *Nr-axSpA*

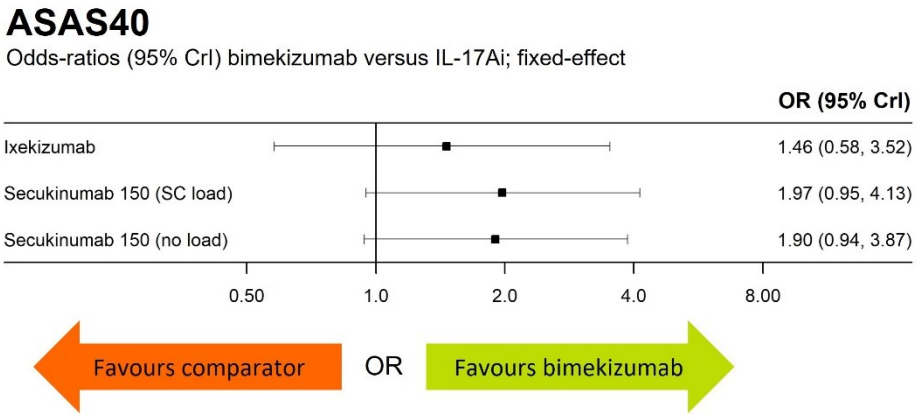
B.3.9.4.1.1 Overview of the included studies

The findings for nr-axSpA are unchanged from the main NMA results as there were no additional studies reporting data for secukinumab 300 mg Q4W (IV load) and secukinumab 150 mg Q4W (IV load) across the key efficacy outcomes. Therefore, the included studies are the same as the main NMA in Section B.3.9.3.1.1 (included studies and the network diagram are provided in Table 20 and Figure 9, respectively).

B.3.9.4.1.2 Predominantly (>50%) b/tsDMARD-naïve network results

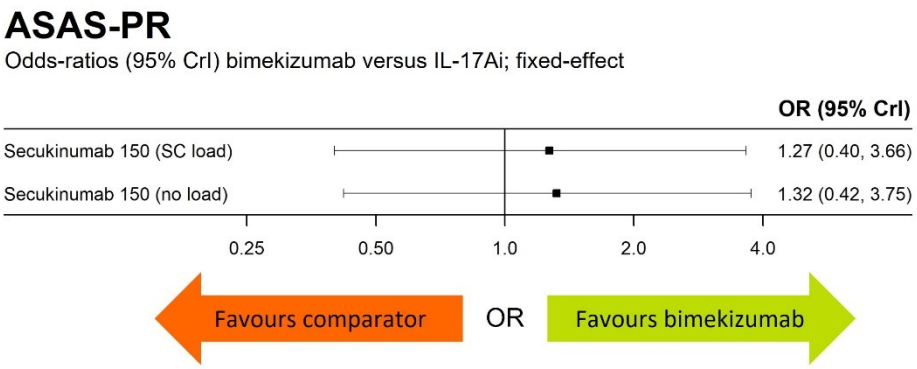
Results for the predominantly b/tsDMARD-naïve network comparisons of bimekizumab vs IL-17A inhibitor comparators in nr-axSpA are summarised in Figure 20, Figure 21, Figure 22, and Figure 23 for the key outcomes ASAS40, ASAS PR, BASDAI50 and BASDAI, respectively.
Bimekizumab was associated with significantly improved change from baseline BASDAI vs ixekizumab in predominantly b/tsDMARD-naïve patients with nr-axSpA. No significant differences were observed between bimekizumab and IL-17A inhibitor comparators for ASAS40, ASAS PR, and BASDAI50. Comparisons vs other treatments in the NMA network across all outcomes are provided in Appendix D.

Figure 20: Forest plot of bimekizumab vs IL-17A inhibitors in predominantly b/tsDMARD-naive patients with nr-axSpA: ASAS40, (binomial outcome, OR 95% CrI)



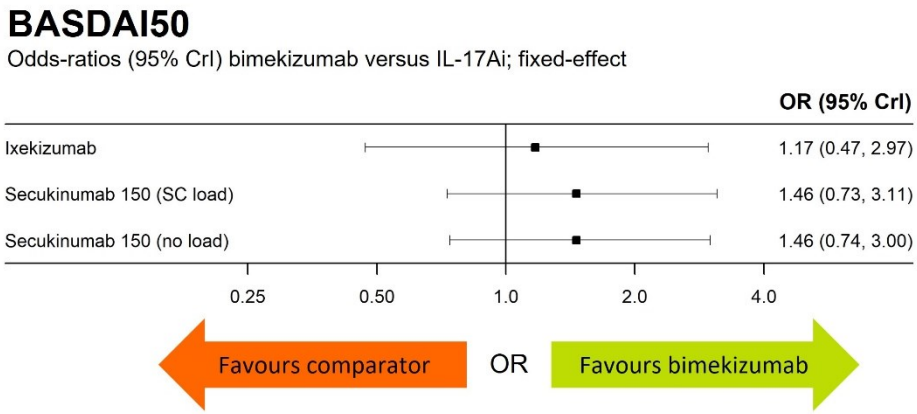
Abbreviations: ASAS40, Assessment of SpondyloArthritis international Society 40% response; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; CrI, credible interval; IL-17Ai, IL-17A inhibitors; nr-axSpA, non-radiographic axial spondyloarthritis; OR, odds ratio.

Figure 21: Forest plot of bimekizumab vs IL-17A inhibitors in predominantly b/tsDMARD-naive patients with nr-axSpA: ASAS PR, (binomial outcome, OR 95% CrI)



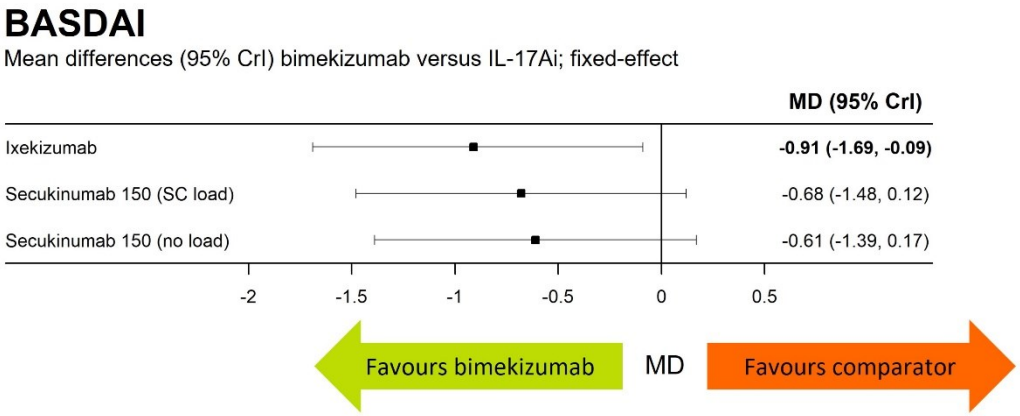
Abbreviations: ASAS PR, Assessment of SpondyloArthritis international Society Partial Remission; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; CrI, credible interval; IL-17Ai, IL-17A inhibitors; nr-axSpA, non-radiographic axial spondyloarthritis; OR, odds ratio.

Figure 22: Forest plot of bimekizumab vs IL-17A inhibitors in predominantly b/tsDMARD-naive patients with nr-axSpA: BASDAI50, (binomial outcome, OR 95% CrI)



Abbreviations: BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50% response; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; CrI, credible interval; ; IL-17Ai, IL-17A inhibitors; nr-axSpA, non-radiographic axial spondyloarthritis; OR, odds ratio.

Figure 23: Forest plot of bimekizumab vs IL-17A inhibitors in predominantly b/tsDMARD-naive patients with nr-axSpA: BASDAI (continuous outcome, MD 95% CrI)



Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CrI, credible interval; IL-17Ai, IL-17A inhibitors; MD, mean difference.

B.3.9.4.2 *AS*

B.3.9.4.2.1 Overview of the included studies

Two additional studies reported data for secukinumab 300 mg Q4W (IV load) and secukinumab 150 mg Q4W (IV load) in the AS population (Table 23). Therefore, this scenario analysis included 28 studies in the predominantly b/tsDMARD-naïve network; two new studies in addition to the 26 studies in the main NMA (Table 22 and Figure 14). The b/tsDMARD-experienced network included 11 studies, two new studies in addition to the nine studies in the main NMA (Table 22 and Figure 15). Note that it was not possible to perform NMA analyses of ASAS PR compared to IL-17A inhibitors comparators in the b/tsDMARD-experienced network due to lack of data. Similarly, it was not possible to perform NMA analyses of BASDAI50 compared to the IV loading doses of IL-17A inhibitor comparators in both networks due to lack of data.

Table 23: Additional studies included in the AS scenario analysis

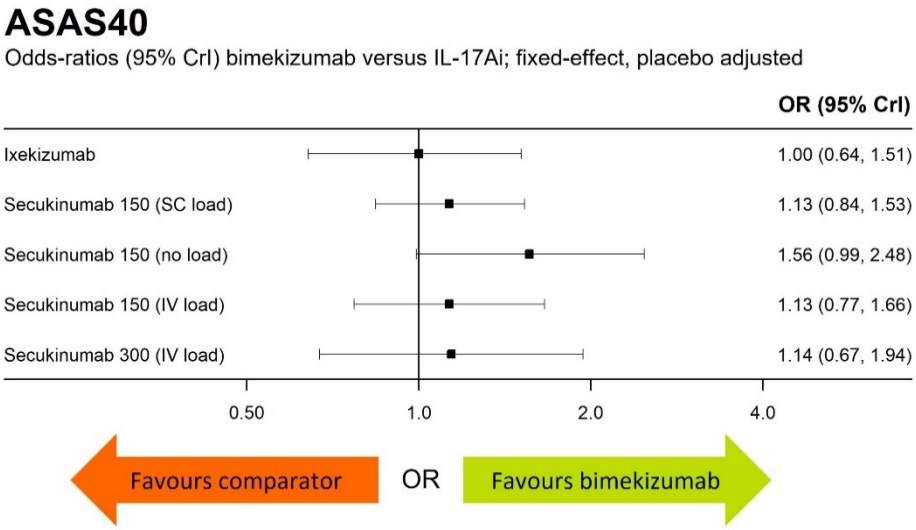
Study	Drug class	Intervention	Predominantly b/tsDMARD-naïve				b/tsDMARD-experienced			
			ASAS40	ASAS PR	BASDAI50	BASDAI	ASAS40	ASAS PR	BASDAI50	BASDAI
MEASURE 1 (62)	IL-17A inhibitor	PBO	✓	✓	×	✓	✓	×	×	✓
		SEC-150 Q4W (IV load)	✓	✓	×	✓	✓	×	×	✓
MEASURE 3 **(61)**		PBO	✓	✓	×	✓	✓	×†	×	✓
		SEC-150 Q4W (IV load)	✓	✓	×	✓	✓	×†	×	✓
		SEC-300 Q4W (IV load)	✓	✓	×	✓	✓	×†	×	✓

†Study reported ASAS PR data, however, it was not possible to perform NMA analyses of ASAS PR versus to IL-17A inhibitor comparators in the b/tsDMARD-experienced network due to small network of studies and too few patients. Moreover, some studies reported zero events in the PBO for these outcomes.
Abbreviations: AS, ankylosing spondylitis; ASAS40, Assessment of SpondyloArthritis international Society 40% response; ASASPR, Assessment of SpondyloArthritis international Society PR, partial remission; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50% response; b/tsDMARD, biological/targeted synthetic disease modifying anti-rheumatic drug; IL, interleukin; IV, intravenous; NMA, network meta-analysis; PBO, placebo; Q4W, every four weeks; SC, subcutaneous SEC, secukinumab.

B.3.9.4.2.2 Predominantly (>50%) b/tsDMARD-naïve network results

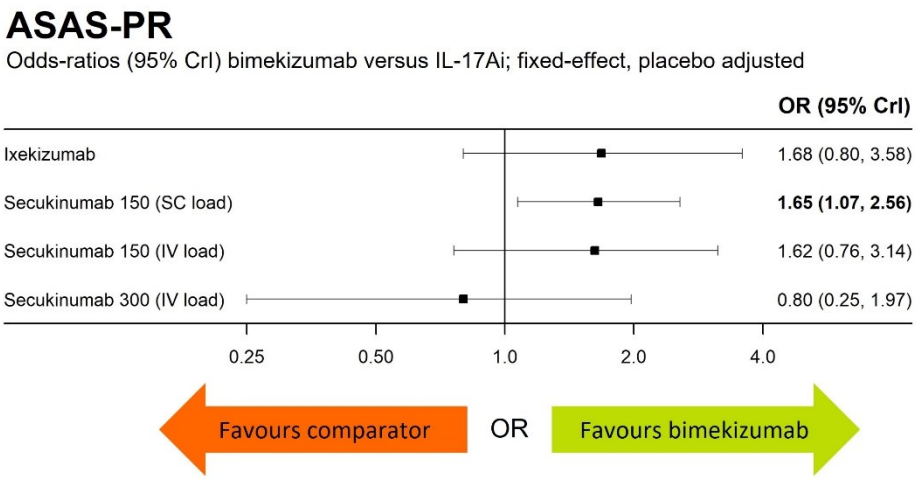
Results for the predominantly b/tsDMARD-naïve network of bimekizumab vs IL-17A inhibitor comparators in AS are summarised in Figure 24, Figure 25, Figure 26, and Figure 27 for the key outcomes of ASAS40, ASAS PR, BASDAI50 and BASDAI, respectively. Bimekizumab was associated with significantly improved ASAS PR vs secukinumab 150 (SC load) in predominantly b/tsDMARD-naïve patients with AS. No significant differences were observed between bimekizumab and IL-17A inhibitor comparators for ASAS40, BASDAI50, and BASDAI. Comparisons vs other treatments in the NMA network across all outcomes are provided in Appendix D.

Figure 24: Forest plot of bimekizumab vs IL-17A inhibitors in predominantly b/tsDMARD-naive patients with AS: ASAS40, (binomial outcome, OR 95% CrI)



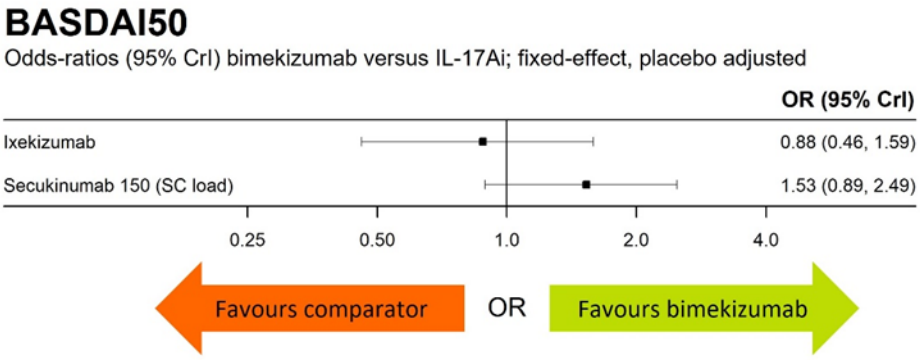
Abbreviations: AS, ankylosing spondylitis; ASAS40, Assessment of SpondyloArthritis international Society 40% response; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; CrI, credible interval; ; IL-17Ai, IL-17A inhibitors; OR, odds ratio.

Figure 25: Forest plot of bimekizumab vs IL-17A inhibitors in predominantly b/tsDMARD-naive patients with AS: ASAS PR, (binomial outcome, OR 95% CrI)



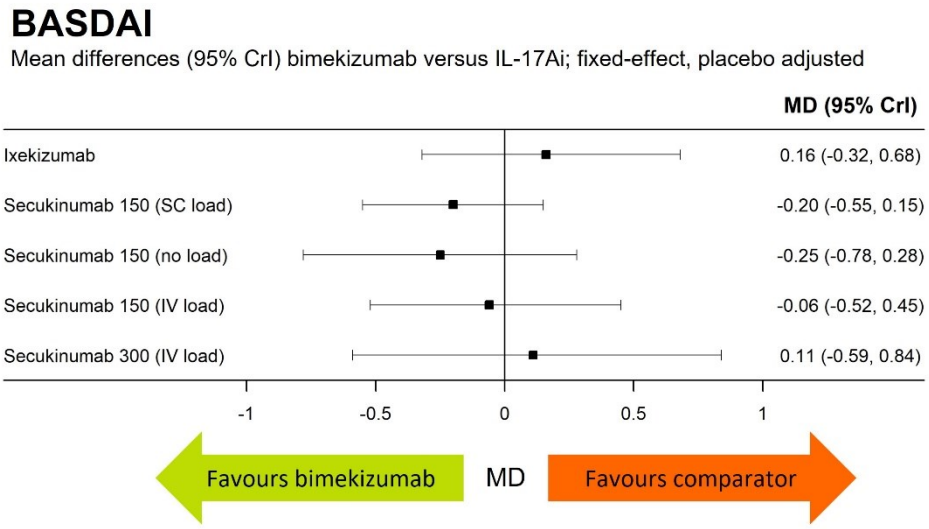
Abbreviations: AS, ankylosing spondylitis; ASAS PR, Assessment of SpondyloArthritis international Society Partial Remission; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; CrI, credible interval; IL-17Ai, IL-17A inhibitors; OR, odds ratio.

Figure 26: Forest plot of bimekizumab vs IL-17A inhibitors in predominantly b/tsDMARD-naive patients with AS: BASDAI50, (binomial outcome, OR 95% CrI)



Abbreviations: AS, ankylosing spondylitis; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50% response; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; CrI, credible interval; IL-17Ai, IL-17A inhibitors; OR, odds ratio.

Figure 27: Forest plot of bimekizumab vs IL-17A inhibitors in predominantly b/tsDMARD-naive patients with AS: BASDAI (continuous outcome, MD 95% CrI)

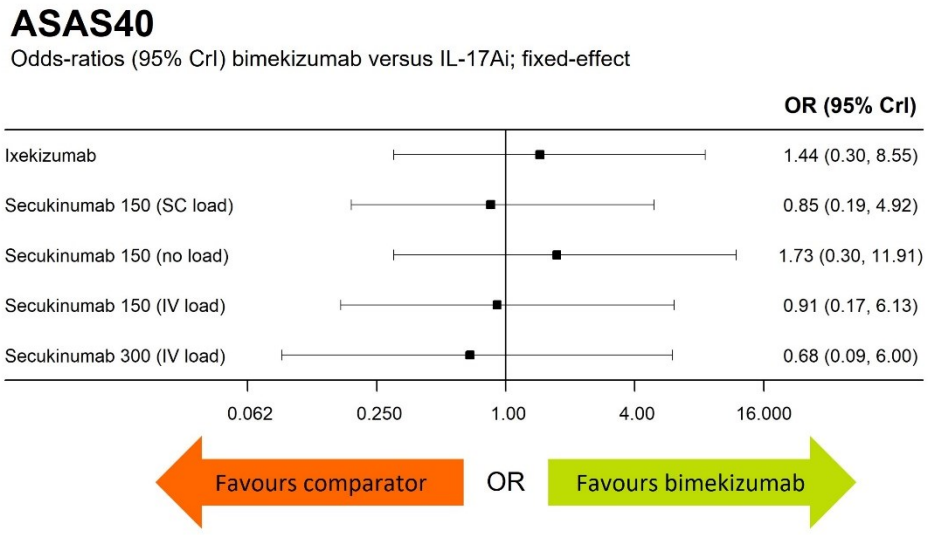


Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CrI, credible interval; IL-17Ai, IL-17A inhibitors; MD, mean difference.

B.3.9.4.2.3 b/tsDMARD experienced network results

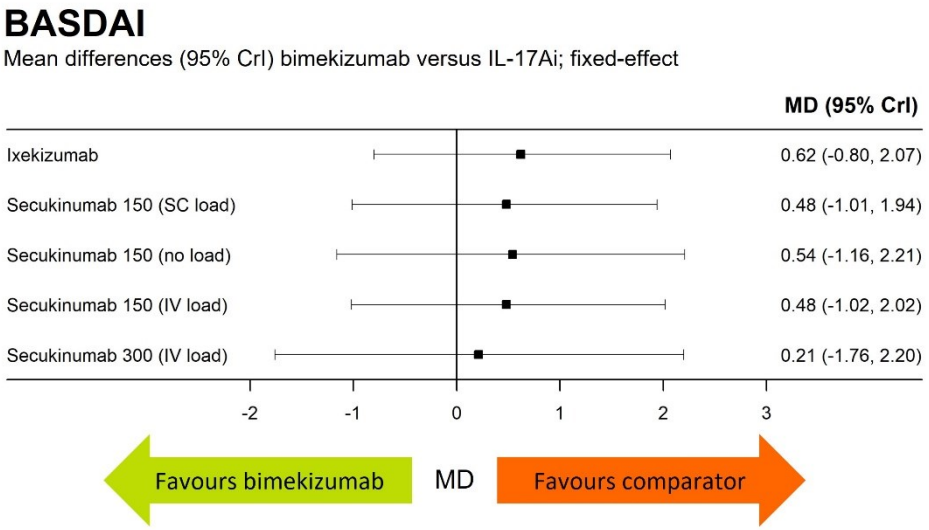
Results for the b/tsDMARD-experienced network of bimekizumab vs IL-17A inhibitor comparators in AS are summarised in Figure 28, and Figure 29 for the two key outcomes that could be analysed, ASAS40 and BASDAI, respectively. No significant differences were observed between bimekizumab and IL-17A inhibitor comparators for ASAS40 and BASDAI. Comparisons vs other treatments in the NMA network across all outcomes are provided in Appendix D.

Figure 28: Forest plot of bimekizumab vs IL-17A inhibitors in b/tsDMARD-experienced patients with AS: ASAS40, (binomial outcome, OR 95% CrI)



Abbreviations: AS, ankylosing spondylitis; ASAS40, Assessment of SpondyloArthritis international Society 40% response; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; CrI, credible interval; OR, odds ratio; IL-17Ai, IL-17A inhibitors.

Figure 29: Forest plot of bimekizumab vs IL-17A inhibitors in b/tsDMARD-experienced patients with AS: BASDAI (continuous outcome, MD 95% CrI)



Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CrI, credible interval; IL-17Ai, IL-17A inhibitors; MD, mean difference.

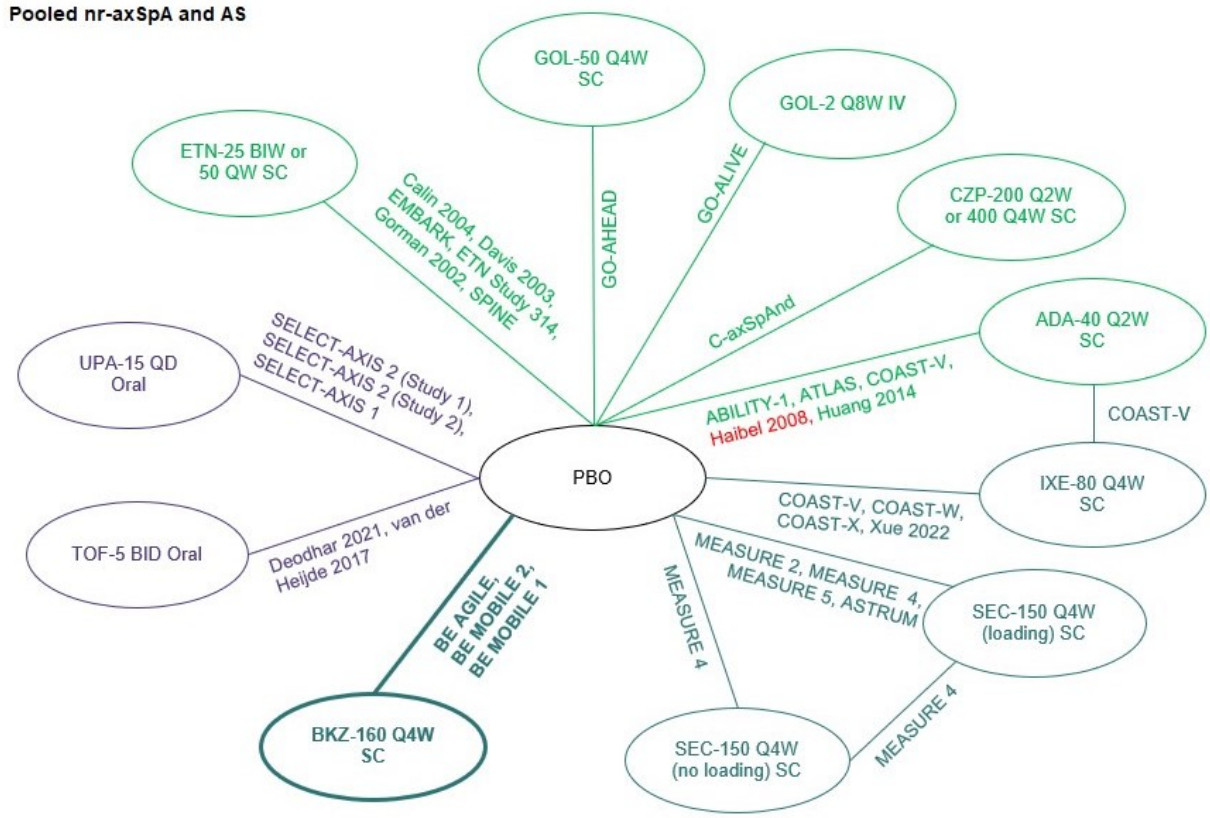
B.3.9.5 NMA safety results

B.3.9.5.1.1 Overview of included studies

In total, 30 studies were included in the safety NMA (included studies and the network diagram are provided in Table 24 and Figure 30, respectively). Seven studies (ASSERT, GO-RAISE, Leeds ETN Study, Hu 2012, Rapid-axSpA, Canadian AS Trial, PREVENT) were excluded from the combined nr-axSpA and AS network due to no tolerability or safety data available in the

Week 12-16 period. Overall, evaluated trials had a low risk of bias; no studies were deemed unsuitable for inclusion in the NMA based on concerns regarding risk of bias.

Figure 30: Network diagram for combined nr-axSpA and AS population



Note: Haibel 2008 was excluded from the NMA analyses, the study did not report discontinuation due to any reason, discontinuation due to AE and it had zero events in both arms for SAEs.
Abbreviations: AS, ankylosing spondylitis; ADA, adalimumab; BID, twice a day; BIW, twice a week; BKZ, bimekizumab; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; IV, intravenous; IXE, ixekizumab; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; Q8W, every 8 weeks; QD, every day; SC, subcutaneous; SEC, secukinumab; TOF, tofacitinib; UPA, upadacitinib.

Table 24: List of studies included in the combined nr-axSpA and AS NMA

Study	Drug class	Intervention	Population	Discontinuation due to any reason	Discontinuation due to AEs	SAEs
BE AGILE (172)	IL-17A/F inhibitor	Bimekizumab 160 mg Q4W SC	Predominantly b/tsDMARD-naïve	✓	✓	✓
BE MOBILE 1 (197)		Bimekizumab 160 mg Q4W SC	Predominantly b/tsDMARD-naïve	✓	✓	✓
BE MOBILE 2 (142, 173)		Bimekizumab 160 mg Q4W SC	Predominantly b/tsDMARD-naïve	✓	✓	✓
COAST-V (174)	IL-17A inhibitor	Ixekizumab 80 mg Q4W SC	b/tsDMARD naïve	✓	✓	✓
COAST-W (175)		Ixekizumab 80 mg Q4W SC	b/tsDMARD-experienced	✓	✓	✓
COAST-X		Ixekizumab 80 mg Q4W SC	b/tsDMARD naïve	✓	✓	✓
Xue 2022 (176)		Ixekizumab 80 mg Q4W SC	b/tsDMARD-experienced	✓	✓	✓
MEASURE 2 (62)		Secukinumab 150 Q4W (SC loading)†	Predominantly b/tsDMARD-naïve	✓	✓	✓
MEASURE 4 (177)		Secukinumab 150 Q4W (SC loading/no loading)†	Predominantly b/tsDMARD-naïve	✓	✓	✓
MEASURE 5 (178)		Secukinumab 150 Q4W (SC loading)†	Predominantly b/tsDMARD-naïve	✓	✓	✓
ASTRUM (179)		Secukinumab 150 Q4W (SC loading)†	Predominantly b/tsDMARD-naïve	✓	✓	✓
Deodhar 2021 (112)	JAK inhibitor	Tofacitinib 5 mg BID oral	Predominantly b/tsDMARD-naïve	✓	✓	✓
van der Heijde 2017 (180)		Tofacitinib 5 mg BID oral	b/tsDMARD naïve	✓	✓	✓
SELECT-AXIS 1 (181)		Upadacitinib 15 mg QD oral	b/tsDMARD naïve	✓	✓	✓

Study	Drug class	Intervention	Population	Discontinuation due to any reason	Discontinuation due to AEs	SAEs
SELECT-AXIS 2 (Study 1) (182)		Upadacitinib 15 mg QD oral	b/tsDMARD-experienced	✓	✓	✓
SELECT-AXIS-2 (Study 2)		Upadacitinib 15 mg QD oral	Predominantly b/tsDMARD-naïve	✓	✓	✓
ABILITY-1	TNF-α inhibitor	Adalimumab 40 mg Q2W SC	b/tsDMARD naïve	✓	✓	✓
ATLAS (183)		Adalimumab 40 mg Q2W SC	b/tsDMARD naïve	✓	✓	×
COAST-V (174)		Adalimumab 40 mg Q2W SC	b/tsDMARD naïve	✓	✓	✓
Haibel 2008		Adalimumab 40 mg Q2W SC	Predominantly naïve	×	×	×†
Huang 2014 (186)		Adalimumab 40 mg Q2W SC	b/tsDMARD naïve	✓	✓	✓
C-axSpAnd		Certolizumab pegol 200 mg Q2W SC	Predominantly b/tsDMARD-naïve	✓	✓	×
Calin 2004 (187)		Etanercept 25 mg BIW SC	b/tsDMARD naïve	✓	✓	✓
Davis 2003 (188)		Etanercept 25 mg BIW SC	b/tsDMARD naïve	✓	×	×
EMBARK		Etanercept 50 mg QW SC	b/tsDMARD naïve	✓	✓	✓
ETN Study 314 (189)		Etanercept 50 mg QW SC or 25 mg BIW SC	b/tsDMARD naïve	✓	✓	✓
Gorman 2002 (190)		Etanercept 25 mg BIW SC	b/tsDMARD naïve	✓	✓	×†
SPINE (192)		Etanercept 50 mg QW SC	b/tsDMARD naïve	×	×	✓
GO-ALIVE (193)		Golimumab 2 mg/kg Q8W IV	Predominantly b/tsDMARD-naïve	×	×†	✓

Study	Drug class	Intervention	Population	Discontinuation due to any reason	Discontinuation due to AEs	SAEs
GO-AHEAD		Golimumab 50 mg Q4W SC	b/tsDMARD naïve	✓	✓	✓

†Refers to secukinumab with or without an initial 150 mg QW loading dose at Weeks 0, 1, 2, 3 and 4; ‡Unknown % of bDMARD-naïve patients, but reasonable to assume >50% patients were bDMARD-naïve. *Study was excluded from the NMA due to zero events in both arms.
Abbreviations: AE, adverse event; AS, ankylosing spondylitis; b/tsDMARD, biological/targeted synthetic disease modifying anti-rheumatic drug; BID, twice daily; BIW, twice weekly; IL, interleukin; IV, intravenous; JAK, Janus kinase; NMA, network meta-analysis; Q2W, every 2 weeks; Q4W, every four weeks; QD, every day; QW, very week; SAE, serious adverse event; SC, subcutaneous.

B.3.9.5.2 *Combined nr-axSpA and AS population results*

Tolerability and safety results for bimekizumab vs ixekizumab in the combined nr-axSpA and AS population are summarised in Table 25. Bimekizumab was associated with similar discontinuation due to any reason, discontinuation due to AE and SAEs compared with ixekizumab.

Comparisons vs other treatments in the NMA network across all outcomes are provided in Appendix D.

Table 25: Tolerability and safety NMA results bimekizumab versus comparator; combined nr-axSpA and AS patient populations

	Discontinuation due to any reason	Discontinuation due to AE	SAEs
Bimekizumab vs ixekizumab OR (95% CrI) (Fixed-effects)	0.97 (0.33, 2.91)	0.65 (0.14, 3.13)	1.18 (0.23, 6.67)

Abbreviations: AE, adverse event; AS, ankylosing spondylitis; CrI, credible interval; nr-axSpA, non-radiographic axial spondyloarthritis; OR, odds ratio; SAEs, serious adverse events.

B.3.9.6 NMA discussion

This SLR and NMA provides an up-to-date synthesis of available evidence for several efficacy, tolerability and safety outcomes for bimekizumab vs ixekizumab for patients with nr-axSpA or AS with inadequate response to, intolerance of, or contraindication to NSAID therapy.

The predominantly bDMARD-naïve network provided the most complete and robust set of results across efficacy outcomes. In the predominantly b/tsDMARD-naïve networks, the proportion of b/tsDMARD-naïve patients included in each study trial ranged from 67%–100% in nr-axSpA and 61%–100% in AS. Across the 10 nr-axSpA and 28 AS studies, the overall proportion of bDMARD-naïve patients was ~90%.

This analysis provides new evidence in b/tsDMARD-experienced patients with AS, albeit with low trial and patient numbers (and hence results should be interpreted with caution). For the b/tsDMARD-experienced network, the comparisons against bimekizumab were based on subgroup data from BE MOBILE 2 and the trial randomisation was not designed to enrol a sufficient number of bDMARD experienced patients to detect a difference between bimekizumab and placebo in this subgroup. A lack of data in bDMARD-experienced patients in axSpA has been observed in previous NICE appraisals in this indication (198, 199).

Furthermore, the b/tsDMARD-experienced network was inadequate for patients with nr-axSpA and contained no data for ixekizumab.

In predominantly b/tsDMARD-naïve patients with nr-axSpA, bimekizumab was associated with significantly improved BASDAI CfB (mean difference: –0.91; 95% CI: –1.69, –0.09) and BASFI (mean difference: –0.86; 95% CI: –1.70, –0.08) vs ixekizumab. For the bDMARD-experienced network in patients with AS, fewer comparisons were possible and no comparisons produced statistically significant differences. No significant differences were observed between bimekizumab and ixekizumab for any other outcome in nr-axSpA or AS.

Overall, based on the scenario analyses that were conducted, no firm conclusion could be made regarding the IV load approach compared with the SC load approach and the impact on the relative efficacy at 16 weeks. Similarly, the maintenance dose of SEC 300 mg Q4W SC (after IV load) is not conclusively shown to be more efficacious than SEC 150 mg Q4W SC (after IV load). It is reasonable to assume that SEC 300 mg Q4W SC (after IV load) is more efficacious than SEC 150 mg Q4W SC (after SC load) initially, but more evidence is required to establish whether the loading schedule impacts on the relative efficacy after 16 weeks.

In addition, bimekizumab and ixekizumab offer a similar tolerability and safety profile across key outcomes. The dual inhibition of IL-17A in addition to IL-17F with bimekizumab may therefore offer a promising treatment option for patients with axSpA, providing similar or improved disease outcomes vs ixekizumab.

B.3.9.7 Uncertainties in the indirect and mixed treatment comparisons

These analyses represent a comprehensive SLR and NMA for axSpA, comparing bimekizumab and ixekizumab over a broad range of efficacy outcomes. This NMA also provides new evidence in b/tsDMARD-experienced patients.

Overall, the nr-axSpA trials (n=10) and AS trials (N=28) included in this NMA were generally well-matched in terms of key baseline characteristics (where reported). However, some uncertainties remain.

Results for the nr-axSpA population are based on a fixed-effect model that may underestimate uncertainty in the treatment effects. There remains an unmet need for a comparative assessment of treatment options for patients with nr-axSpA with inadequately controlled disease following treatment with NSAIDs and one or more biological treatment. Some outcome data are available from the BE MOBILE 1 study for the bDMARD-experienced subgroup, albeit for a small group of patients (10 patients in the bimekizumab arm and 17 for placebo). However, bDMARD experienced data for the comparators in nr-axSpA is limited, with no trial data available for ixekizumab in bDMARD experienced patients with nr-axSpA.

In the AS population, the fixed-effect placebo adjusted model provided the most reliable results compared with the random effects models. This may underestimate uncertainty in the treatment effects. For the bDMARD-experienced network, the comparisons against bimekizumab were based on subgroup data from BE MOBILE 2, and the trial was not powered to detect a difference between bimekizumab and placebo in the bDMARD-experienced subgroup. There were few patients in the placebo arm of BE MOBILE 2 (17 patients), which is the connecting node for the indirect comparisons with bimekizumab. Therefore, all comparisons with bimekizumab are subject to imprecision and the analysis did not detect meaningful differences between active comparators.

In the scenario analysis approximating the efficacy of the 300 mg Q4W SC and then the impact of IV loading versus SC, data from MEASURE 1 and MEASURE 3 were added to the AS networks. The analysis for the bDMARD-experienced network was associated with large 95% CIs, and therefore subject to significant uncertainty. No inferences can be made on differential treatment effects between loading dose regimens. More evidence is required to establish whether the loading schedule impacts on relative efficacy after 16 weeks.

The classification criteria for nr-axSpA are based on the ASAS axSpA classification criteria published in 2009 (83), and as such there are few trials published to date for this indication compared to AS, and few publications with which to cross-validate the results of this NMA. The current NMA broadly aligns with the SEC nr-axSpA NICE single technology appraisal (TA719), although results cannot be compared since these were redacted (200). In addition, the broad date range of available of included studies (nr-axSpA publication date range: 2008–2022; AS publication date range: 2002–2022), means that b/tsDMARDs were available for some, but not all, patients included, which may have an impact on interpretation of results.

B.3.10 Adverse reactions

Phase 3 BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS) trials demonstrated that bimekizumab was well tolerated in the double-blind period vs placebo (16 weeks) and in the overall treatment period (52 weeks), consistent with early phase trials of bimekizumab in these patient populations (47, 141, 142, 144).

- During the double-blind treatment period of both trials, adverse events (AEs) were reported at a higher incidence in the bimekizumab groups compared with placebo groups (BE MOBILE 1: 80 patients [62.5%] vs 71 patients [56.3%], BE MOBILE 2: 120 patients [54.3%] vs 48 [43.2%], respectively) (Section B.3.10.1).
- The most commonly reported AEs with bimekizumab in the double-blind and overall periods in both trials were nasopharyngitis, upper respiratory tract infection, and oral candidiasis (Section B.3.10.1).
- The incidence of AEs leading to study discontinuation was low in both trials and the risk of experiencing an AE did not increase with longer exposure to bimekizumab (Section B.3.10.1).
- The incidence of serious adverse events (SAEs) was low in both trials, and none led to study discontinuation (Section B.3.10.1).
- The incidence of drug-related AEs was higher in the bimekizumab group compared with placebo (32 patients [25.0%] vs 18 patients [14.3%] in BE MOBILE 1 and 65 patients [29.4%] vs 19 patients [17.1%] in BE MOBILE 2, respectively) (Section B.3.10.1.2).
- In both trials, the most commonly reported drug-related AE with bimekizumab was oral candidiasis. All fungal infections were localised, and mild or moderate (with the exception of one event in BE MOBILE 1). The overall incidence of serious drug-related AEs was low in both trials (Section B.3.10.1.2)
- No major adverse cardiac events (MACE), active tuberculosis, or anaphylactic reactions were reported at the time of the Week 52 data cut-off in BE MOBILE 1 or BE MOBILE 2 (Section B.3.10.1.3).

The BE AGILE and BE AGILE 2 trial in AS demonstrated that the favourable safety profile of bimekizumab was maintained over 156 weeks (Section B.3.10.2)

- From Weeks 0–156, AEs were reported by 92.4% of patients (49.2% were drug-related); the most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, and bronchitis.
- The incidence of SAEs and AEs leading to study discontinuation was low in both trials, and the risk of experiencing an AE did not increase with longer exposure to bimekizumab.
- No cases of active tuberculosis were reported, and other AEs of interest were infrequent (including active inflammatory bowel disease, anterior uveitis, and adjudicated MACE).

B.3.10.1 Primary safety evidence (BE MOBILE 1 and BE MOBILE 2)

B.3.10.1.1 *Safety analysis at Week 16 and Week 52*

Safety evidence is available for the 16-week double blind period (bimekizumab vs placebo) and for the overall period at the Week 52 data cut-off (BE MOBILE 1: 1st July 2022; BE MOBILE 2: 31st May 2022). The overall period presents data from all study participants who received bimekizumab, including those randomised to the bimekizumab group at baseline, those who switched from placebo to bimekizumab at Week 16, and safety data from the safety-follow up

period for a small subset of patients who did not enter the open-label extension study or had a delayed entry due to the COVID-19 pandemic.

The total duration of exposure was similar between the bimekizumab and placebo groups during the double-blind period in BE MOBILE 1 (40.4 and 38.1 patient-years, respectively), and was 197.0 patient-years with bimekizumab in the overall treatment period (141). In BE MOBILE 2, the total duration of exposure was higher with bimekizumab than placebo during the double-blind period due to the 2:1 randomisation study design (68.3 patient-years and 34.6 patient-years, respectively), and 276.2 patient-years with bimekizumab in the overall treatment period (142).

During the double-blind treatment period of both trials, AEs were reported at a higher incidence in the bimekizumab groups compared with placebo groups (BE MOBILE 1: 80 patients [62.5%] vs 71 patients [56.3%], BE MOBILE 2: 120 patients [54.3%] vs 48 [43.2%], respectively) (Table 26) (141, 142). In the overall period of both trials, the exposure-adjusted incidence rates (EAIRs) of AEs with bimekizumab did not increase over time from the double-blind treatment period, indicating that the risk of experiencing an AE does not increase with longer exposure to bimekizumab (141, 142). Notably, treatment with bimekizumab was associated with a lower incidence of acute anterior uveitis compared with placebo, suggesting a potential effect on preventing uveitis flares in patients with axSpA (Table 26) (141, 142).

The most commonly reported AEs with bimekizumab in the double-blind and overall periods in BE MOBILE 1 and BE MOBILE 2 were nasopharyngitis, upper respiratory tract infection, and oral candidiasis (Table 27) (141, 142). However, the majority of AEs were mild or moderate in both treatment periods in BE MOBILE 1 and BE MOBILE 2. The incidence of serious adverse events (SAEs) was low in both trials, and none led to study discontinuation. No deaths occurred in the trials (141, 142).

The incidence of AEs leading to discontinuation was low in both trials; in BE MOBILE 1, two patients (1.6%) in the bimekizumab group vs five patients (4.0%) in the placebo group during the double-bling period discontinued due to AEs, and six patients (2.5%) discontinued in the bimekizumab group at Week 52 (141). In BE MOBILE 2, six patients (2.7%) in the bimekizumab group and no patients in the placebo group discontinued due to AEs during the double-bling period, and 15 patients (4.5%) discontinued in the bimekizumab group at Week 52 (Table 26) (142).

Table 26: Overall summary of AEs (safety set)

Category, n (%)†‡	BE MOBILE 1 (nr-axSpA)			BE MOBILE 2 (AS)		
	Double-blind period (16 weeks)		Overall period (52 weeks)	Double-blind period (16 weeks)		Overall period (52 weeks)
	Bimekizumab 160 mg Q4W n=128	Placebo n=126	Bimekizumab 160 mg Q4W n=244	Bimekizumab 160 mg Q4W n=221	Placebo n=111	Bimekizumab 160 mg Q4W n=330
Any AEs	80 (62.5)	71 (56.3)	183 (75.0)	120 (54.3)	48 (43.2)	249 (75.5)
Severe AEs	0	1 (0.8)	8 (3.3)	4 (1.8)	0	14 (4.2)
Study discontinuations due to AEs‡	2 (1.6)	5 (4.0)	6 (2.5)	6 (2.7)	0	15 (4.5)
Drug-related AEs	33 (25.8)	17 (13.5)	81 (33.2)	65 (29.4)	19 (17.1)	135 (40.9)
Serious AEs	0	1 (0.8)	9 (3.7)	4 (1.8)	1 (0.9)	20 (6.1)
Deaths	0	0	0	0	0	0

Source: van der Heijde et al 2023 (47) and Baraliakos et al 2022 (144).
†n=number of study participants who reported at least 1 AE in that category; ‡Includes patients who switched from placebo to bimekizumab (events after switch only).
Abbreviations: EAIR, exposure-adjusted incidence rate; PT, preferred term; Q4W, every 4 weeks.

Table 27: Incidence of AEs based on most common PTs reported by ≥5% of patients (safety set)

N, % [EAIR/100 PY]†‡	BE MOBILE 1 (nr-axSpA)			BE MOBILE 2 (AS)		
	Double-blind period (16 weeks)		Overall period (52 weeks)	Double-blind period (16 weeks)		Overall period (52 weeks)
	Bimekizumab 160 mg Q4W n=128	Placebo n=126	Bimekizumab 160 mg Q4W n=244	Bimekizumab 160 mg Q4W n=221	Placebo n=111	Bimekizumab 160 mg Q4W n=330
Eye disorders	3 (2.3) [7.5]	8 (6.3) [21.3]	–	5 (2.3) [7.4]	7 (6.3) [21.0]	–
Gastrointestinal disorders	–	–	33 (13.5) [17.4]	29 (13.1) [46.5]	11 (9.9) [33.6]	77 (23.3) [31.3]
Diarrhoea	–	–	–	7 (3.2) [10.5]	1 (0.9) [2.90]	18 (5.5) [6.5]
General disorders and administration site conditions	–	–	26 (10.7) [13.5]	–	–	–
Infections and infestations	46 (35.9) [144.8]	31 (24.6) [94.4]	127 (52.0) [94.0]	61 (27.6) [108.1]	25 (22.5) [83.7]	151 (45.8) [75.7]
Oral candidiasis	4 (3.1) [10.1]	0	18 (7.4) [9.0]	10 (4.5) [14.9]	0	20 (6.1) [7.2]
Nasopharyngitis	13 (10.2) [34.1]	6 (4.8) [16.3]	30 (12.3) [15.7]	17 (7.7) [26.2]	4 (3.6) [11.7]	30 (9.1) [11.0]
Upper respiratory tract infection	9 (7.0) [23.1]	10 (7.9) [27.4]	23 (9.4) [11.9]	6 (2.7) [9.0]	8 (7.2) [24.3]	21 (6.4) [7.5]
Corona virus infection	–	–	17 (7.0) [8.3]	–	–	–
Musculoskeletal and connective tissue disorders	–	–	44 (18.0) [24.0]	–	–	47 (14.2) [17.7]
Nervous system disorders	–	–	28 (11.5) [14.6]	18 (8.1) [28.1]	5 (4.5) [15.0]	36 (10.9) [13.5]
Headache	–	–	13 (5.3) [6.5]	9 (4.1) [13.6]	5 (4.5) [15.0]	18 (5.5) [6.5]
Skin and subcutaneous tissue disorders	–	–	–	–	–	63 (19.1) [24.8]
Vascular disorders	–	–	–	–	–	18 (5.5) [6.3]

Source: van der Heijde et al 2023 (47), Baraliakos et al 2022 (144); UCB, Data on File BE MOBILE 1 (2022) (141); UCB Data on File BE MOBILE 2 (2022) (142).
†n=number of patients who reported ≥1 AE within PT; ‡Includes patients who switched from placebo to bimekizumab (events after switch only).
Abbreviations: EAIR, exposure-adjusted incidence rate; PT, preferred term; Q4W, every 4 weeks.

B.3.10.1.2 *AEs suspected of being drug-related*

During the double-blind periods of BE MOBILE 1 and BE MOBILE 2, the incidence of drug-related AEs (as determined by the Investigator) was higher in the bimekizumab group compared with placebo (32 patients [25.0%] vs 18 patients [14.3%] in BE MOBILE 1 and 65 patients [29.4%] vs 19 patients [17.1%] in BE MOBILE 2, respectively) (141, 142). In both trials, the most commonly reported drug-related AE with bimekizumab was oral candidiasis (BE MOBILE 1: four patients [3.1%] and 14 patients [5.7%] in the double-blind and overall periods, respectively; BE MOBILE 2: nine patients [4.1%] and 18 patients [5.5%] in the double-blind and overall periods, respectively) (141, 142). However, all fungal infections were localised and mild or moderate (with the exception of one event of oral candidiasis in BE MOBILE 1). In BE MOBILE 1 there were no serious drug-related AEs during the double-blind treatment period (0.0%), and one during the overall treatment period (0.4%). In BE MOBILE 2 the overall incidence of serious drug-related AEs with bimekizumab was low during the double-blind (two patients [0.9%]) and overall treatment period (seven patients [2.1%]) (Appendix E) (141, 142).

B.3.10.1.3 *Other safety topics of interest*

No major adverse cardiac event (MACE), active tuberculosis, or anaphylactic reactions were reported at the time of the Week 52 data cut-off in BE MOBILE 1 or BE MOBILE 2 (141, 142). All fungal infections were nonserious, mild to moderate in severity, localised (with the exception of one event of oral candidiasis in BE MOBILE 1), and few fungal infections led to discontinuation. There was one malignancy in the bimekizumab group in BE MOBILE 1 (clear cell renal cell carcinoma) and one in BE MOBILE 2 (melanoma), neither were considered drug-related. Events of neutropenia reported with bimekizumab were mild or moderate (one patient in the double blind period of each of BE MOBILE 1 and BE MOBILE 2, two patients in the BE MOBILE 1 overall treatment period, and three patients in the BE MOBILE 2 overall treatment period, no patients in the placebo group of either trial). Event rates were comparable between the treatment arms.

During BE MOBILE 1 seven patients in the double-blind period, and 20 patients in the overall period reported a hepatic event in the bimekizumab group (141). In BE MOBILE 2, ten patients in the double-blind period, and 33 patients overall treatment periods reported a hepatic event. Event rates were comparable between the treatment arms (142). All hepatic event TEAEs reported were nonserious, mild or moderate in severity, and none led to study discontinuation.

The most commonly reported hepatic events in the double-blind period of BE MOBILE 1 were transaminases increased (three patients [2.3%]), and AST increased and hepatic steatosis (two patients [1.6%] each), and ALT increased and AST increased (three patients [1.4%] each) in BE MOBILE 2. During the overall period, the most commonly reported hepatic events in BE MOBILE

1 were AST increased (seven patients [2.9%]), and ALT increased (six patients [1.8%]) and AST increased (five patients [1.5%]) in BE MOBILE 2 (141, 142).

These events were mostly mild to moderate in severity and did not lead to study discontinuation (Appendix E).

B.3.10.2 Supporting safety evidence (BE AGILE and BE AGILE 2)

A total of 4,821 patients have been treated with bimekizumab in blinded and open-label clinical studies in PSO, PsA, and axSpA (nr-axSpA and AS) representing 8733.0 patient-years of exposure. Of these, over 3,900 patients were exposed to bimekizumab for at least one year. Overall, the safety profile of bimekizumab is consistent across all indications. The most frequently reported adverse reactions were upper respiratory tract infections (14.5%, 14.6%, 16.3% in PSO, PsA, and axSpA, respectively) and oral candidiasis (7.3%, 2.3%, 3.7% in PSO, PsA, and axSpA, respectively) (Appendix C).

Long-term safety evidence with bimekizumab in AS is available from the Phase 2b RCT (BE AGILE) and its open-label extension study (BE AGILE 2).

B.3.10.2.1 *Safety data up to Week 156*

Exposure to bimekizumab over 156 weeks among all patients randomised at baseline was 815.6 patients years (PY), including 554.7 PY during BE AGILE 2 (Weeks 48–156) (147). For the total treatment period, AEs were observed in 280 (92.4%) patients and SAEs were observed in 43 (14.2) patients (147). The most commonly reported AEs were nasopharyngitis (18.8%) and upper respiratory tract infection (12.2%) (147). For the majority of AEs that presented in more than one patient, EAIRs did not increase from Weeks 0–48 to Weeks 48–156. Study discontinuations due to AEs were infrequent (37 [12.2%]) during the 156-week study period, including 14 patients during BE AGILE 2. (147) Study discontinuation due to AEs during BE AGILE 2 were most commonly due to infections and elevated liver enzymes; however, elevated liver enzymes were generally mild to moderate, and none met Hy's Law criteria. One death was reported during Weeks 0–48 (cardiac arrest in a patient with cardiovascular risk factors) and one during BE AGILE 2 study (road traffic accident); neither was considered treatment-related (Table 28).

A total of 22.1% of patients had a fungal infection during Weeks 0–156; all fungal infections were assessed as mild to moderate and all, but one did not lead to discontinuation. There were no patients with serious or systemic fungal infections. No cases of active tuberculosis were reported, and other AEs of interest were infrequent (including active inflammatory bowel disease, anterior

uveitis, and adjudicated MACE). Detailed results for safety topics of interest are presented in Appendix E.

Table 28: Long-term safety exposure to bimekizumab in patients with AS

	BE AGILE	BE AGILE 2	BE AGILE and BE AGILE 2
n (%) [EAIR/100 PY]	**Week 0–48† N=303; 261.3 PY**	**Week 48–156‡ N=303; 554.7 PY**	**Week 0–156†‡ N=303; 815.6 PY**
Any AE	235 (77.6) [186.2]	215 (84.3) [110.8]	280 (92.4) [141.0]
Most frequently reported TEAEs (≥5%) by preferred term			
Nasopharyngitis	34 (11.2) [13.7]	34 (13.3) [6.7]	57 (18.8) [8.1]
Upper respiratory tract infection	17 (5.6) [6.7]	24 (9.4) [4.6]	37 (12.2) [5.0]
Bronchitis	18 (5.9) [7.1]	15 (5.9) [2.8]	33 (10.9) [4.4]
Pharyngitis	18 (5.9) [7.1]	15 (5.9) [2.8]	29 (9.6) [3.8]
ALT increased	13 (4.3) [5.1]	15 (5.9) [2.8]	23 (7.6) [3.0]
Oral candidiasis	16 (5.3) [6.3]	13 (5.1) [2.4]	23 (7.6) [3.0]
Hypercholesterolemia	12 (4.0) [4.7]	11 (4.3) [2.0]	20 (6.6) [2.6]
Hypertension	10 (3.3) [3.9]	11 (4.3) [2.0]	20 (6.6) [2.6]
Rhinitis	14 (4.6) [5.5]	6 (2.4) [1.1]	20 (6.6) [2.6]
Tonsillitis	8 (2.6) [3.1]	13 (5.1) [2.4]	19 (6.3) [2.4]
Arthralgia	8 (2.6) [3.1]	11 (4.3) [2.0]	18 (5.9) [2.3]
Conjunctivitis	10 (3.3) [3.9]	10 (3.9) [1.8]	18 (5.9) [2.3]
Headache	13 (4.3) [5.1]	6 (2.4) [1.1]	18 (5.9) [2.3]
Respiratory tract infection	11 (3.6) [4.3]	8 (3.1) [1.5]	18 (5.9) [2.3]
GGT increased	13 (4.3) [5.1]	5 (2.0) [0.9]	17 (5.6) [2.2]
Oral fungal infection	14 (4.6) [5.5]	8 (3.1) [1.5]	16 (5.3) [2.1]
AST increased	9 (3.0) [3.5]	9 (3.5) [1.6]	16 (5.3) [2.0]
SAEs	13 (4.3) [5.1]	31 (12.2) [5.9]	43 (14.2) [5.6]
Study discontinuations due to AEs	20 (6.6)	14 (5.5)	37 (12.2)
Drug-related AEs	110 (36.3)	90 (35.3)	149 (49.2)
Deaths	1 (0.3)	1 (0.4)	2 (0.7)

Source: Baraliakos, (2022) (147).
†At baseline, patients were randomised 1:1:1:1:1 to receive subcutaneous bimekizumab 16 mg, 64 mg, 160 mg, or 320 mg or placebo Q4W. At Week 12, patients initially randomised to bimekizumab 16 mg, 64 mg, or placebo were re-randomised 1:1 to bimekizumab 160 mg or 320 mg Q4W through Week 48, while patients initially randomised to bimekizumab 160 mg or 320 mg continued their dosing to Week 48.‡ All patients in the open-label extension (BE AGILE 2) received open-label bimekizumab 160 mg Q4W, regardless of prior dosing regimen.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EAIR, exposure-adjusted incidence rate; GGT, gamma-glutamyl transferase increased; PY, patient-years; Q4W, every 4 weeks; SAE, serious adverse event; TEAE, treatment emergent adverse event.

B.3.11 Conclusions about comparable health benefits and tolerability / safety

Bimekizumab is the only available humanised immunoglobulin monoclonal antibody that selectively inhibits IL-17F in addition to IL-17A in order to inhibit the IL-17 pathway, a pivotal driver of inflammation in axSpA (45, 46). Bimekizumab is expected to be positioned first-line (after NSAID failure) in patients who are contraindicated to TNF-α inhibitors, and second-line and later for all other patients with axSpA. Ixekizumab is considered the most relevant comparator for bimekizumab as it is the most similar treatment, in terms of efficacy, tolerability and safety, in the NMA (Appendix D) and the most likely treatment to be displaced by bimekizumab in axSpA. Clinical experts expected that bimekizumab would be grouped alongside ixekizumab in UK clinical practice (35).

The Phase 3 trial programme of bimekizumab met its primary endpoint (ASAS40 at Week 16), and also reported significant improvements in stringent outcomes (ASAS40, ASAS PR, ASDAS-MI) disease activity (BASDAI), physical function (BASFI), pain (NSP), fatigue (FACIT), and QoL (ASQoL), compared with placebo in patients with axSpA (47, 141, 142). Additionally, more patients receiving bimekizumab achieved ASDAS <2.1 (ASDAS LDA) than with placebo, demonstrating that bimekizumab can lead to a large proportion of patients meeting stringent and clinically relevant treatment targets (201). The BE MOBILE trials also provide evidence to suggest that bimekizumab is efficacious in patients with axSpA regardless of prior TNF-α inhibitor exposure. Importantly, these treatment responses were sustained until Week 52 while maintaining a favourable safety profile, and no new or unexpected safety concerns were observed.

The populations of both trials generally align with UK clinical practice, the axSpA patient population, and the ixekizumab appraisal (TA718) (8, 54). These results also add to the developing evidence demonstrating the efficacy of bimekizumab in rheumatology, including both the BE OPTIMAL and BE COMPLETE Phase 3 trials in patients with PsA (202, 203), and the four Phase 3 trials in patients with PSO (BE VIVID, BE READY, BE SURE, and BE RADIANT) (204-207).

Although direct comparisons between bimekizumab and IL-17A inhibitors cannot be made using data from BE MOBILE 1 and BE MOBILE 2, evidence for the efficacy of bimekizumab is supported by the NMAs conducted in Section B.3.9. Bimekizumab was associated with significantly improved change from baseline BASDAI and BASFI vs ixekizumab in predominantly b/tsDMARD-naïve patients with nr-axSpA and no significant differences were observed between bimekizumab and ixekizumab for any other outcome in nr-axSpA or AS. In no comparisons was

bimekizumab statistically significantly worse than ixekizumab. The dual inhibition of IL-17A in addition to IL-17F with bimekizumab may therefore offer a promising treatment option for patients with axSpA, providing similar or improved disease outcomes vs ixekizumab.

Bimekizumab also demonstrated comparable tolerability and safety when considering discontinuation due to any reason, discontinuation due to AE and occurrence of SAEs in a combined nr-axSpA and AS patient population, compared with all treatments in the network (Section B.3.9.4).

Taken together, the results of the clinical trial programme and the NMAs demonstrate that treatment with bimekizumab resulted in rapid, clinically relevant improvements in disease manifestations, and was well tolerated. Bimekizumab may therefore offer patients with axSpA an effective treatment option with a novel mode of action.

B.3.12 Ongoing studies

BE AGILE 2 (Section B.3.3.2 and Appendix) is ongoing, with 5-year data expected end of 2023.

BE MOVING is an ongoing open-label extension study to evaluate the long-term safety, tolerability, and efficacy of bimekizumab in patients with nr-axSpA and AS. Participants enrolled into BE MOVING following completion of BE MOBILE 1 or BE MOBILE 2, and receive bimekizumab throughout the study (148).

B.4 Cost-comparison analysis

A cost-comparison analysis was conducted comparing bimekizumab against ixekizumab, secukinumab 150 mg, and secukinumab 300 mg in patients with non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS).

- The analysis considers costs associated with drug acquisition only.
- Administration, monitoring, disease management and adverse event (AE) costs are expected to be equivalent between bimekizumab, ixekizumab, secukinumab 150 mg and secukinumab 300 mg.
- The results are presented using the patient access scheme (PAS) price for bimekizumab, and list prices for ixekizumab and secukinumab as the PAS discounts for ixekizumab and secukinumab are not known.
- Assuming PAS price for bimekizumab and list prices for ixekizumab and secukinumab, over a 10-year time horizon bimekizumab is associated with:
    - Cost savings compared to ixekizumab of £[redacted] and £[redacted] for the nr-axSpA and AS populations, respectively
    - Incremental costs compared to secukinumab 150 mg of £[redacted] and £[redacted] for the nr-axSpA and AS populations, respectively
    - Cost savings compared to secukinumab 300 mg of £[redacted] and £[redacted] for the nr-axSpA and AS populations, respectively
- All considered scenario analyses result in bimekizumab being cost-saving compared with ixekizumab and secukinumab 300 mg in both nr-axSpA and AS patients, and associated with similar costs compared to secukinumab 150 mg.

Bimekizumab is associated with similar efficacy and safety to ixekizumab and secukinumab (Section B.3.9 and Appendix D); a cost-comparison analysis is therefore presented. Ixekizumab is considered to be the most relevant comparator for this appraisal (Section B.1.1.1).

B.4.1 Changes in service provision and management

The cost-comparison analysis includes drug acquisition costs only. A summary of included costs is presented in Table 29. No NHS service changes are anticipated upon approval of bimekizumab for treating axSpA.

Table 29: Included cost types

Cost type	Included in analysis	Rationale
Drug acquisition	Yes	Unit costs differ between bimekizumab, ixekizumab and secukinumab, and both ixekizumab and secukinumab are associated with loading doses.
Administration	No	Administration costs are equivalent between bimekizumab, ixekizumab and secukinumab; all three treatments require an initial training session with a nurse for subcutaneous administration, after which the treatments are self-administered at home.
Monitoring	No	No additional monitoring requirements are anticipated for bimekizumab in addition to those required for ixekizumab or secukinumab.
Disease management	No	Disease management costs are expected to be the same or lower for bimekizumab compared with ixekizumab and secukinumab, given that bimekizumab is associated with similar or improved BASFI versus ixekizumab and secukinumab (Section B.3.9 and Appendix D); BASFI has been the basis for disease management cost equations used in previous appraisals (54, 76, 122).
Adverse events	No	The safety profiles of bimekizumab, ixekizumab and secukinumab are similar based on the NMA (Section B.3.9.5 and Appendix D). In BE MOBILE 1 there were no serious drug-related AEs during the double-blind treatment period, and one during the overall treatment period. In BE MOBILE 2 the overall incidence of serious drug-related AEs with bimekizumab was low during the double-blind (two patients [0.9%]) and overall treatment period (seven patients [2.1%]) (Appendix E).

Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

B.4.2.1.1 *Decision problem*

The decision problem for the cost-comparison analysis is presented in Table 30.

Table 30: Decision problem

Component	Approach
Population	• Patients with active AS who have responded inadequately or are intolerant to conventional therapy (NSAIDs and physiotherapy) or TNF-α inhibitors • Patients with active nr-axSpA for whom NSAIDs or TNF-α inhibitors have been inadequately effective or not tolerated, or are contraindicated
Intervention	Bimekizumab
Comparator	• Ixekizumab • Secukinumab 150 mg • Secukinumab 300 mg†
Outcome	• Incremental costs per patient • Total costs per patient, by type of cost
Perspective	NHS and PSS in England and Wales
Time horizon	10 years • Scenario analyses consider time horizons of 1 year, 2 years and 5 years
Discounting	No discounting • A scenario analysis is considered in which an annual rate of 3.5% is applied

†Secukinumab 300 mg is included as a comparator in both the AS and nr-axSpA populations, given that this dose is used in clinical practice in both populations (Section B.1.1.1) (35, 58).
Abbreviations: AS, ankylosing spondylitis; NHS, National Health Service; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, nonsteroid anti-inflammatory drug; PSS, personal social services; TNF-α, tumour necrosis factor-alpha.

B.4.2.1.2 *Model methods*

A cost-comparison model was developed in Microsoft® Excel, considering drug acquisition costs only. In each 4-week model cycle[k], the proportion of patients remaining on treatment was determined in order to calculate drug acquisition costs.

At 16 weeks for bimekizumab and secukinumab (150 mg and 300 mg), and 16–20[l] weeks for ixekizumab, the proportion of patients who do not achieve BASDAI50 ('non-responders') are assumed to discontinue treatment. Scenarios are considered in which response is assessed at 16 weeks for all comparators, and in which response is assessed based on ASAS40. Given that bimekizumab, ixekizumab, secukinumab 150 mg and secukinumab 300 mg are associated with similar efficacy (Section B.3.9 and Appendix D), the proportion of responders is assumed to be the same between the four treatments, but assumed to differ between nr-axSpA and AS (Table 31).

[k] A 4-week cycle length is used in the model to align with the dosing schedule for bimekizumab.
[l] Half of the non-responders are assumed to discontinue at Week 16, and half are assumed to discontinue at Week 20.

Table 31: BASDAI50 and ASAS40 response rates

	BASDAI50 response	ASAS40 response	Source
Nr-axSpA	46.9%	47.7%	BE MOBILE 2 (142)
AS	46.6%	44.8%	BE MOBILE 1 (141)

Abbreviations: AS, ankylosing spondylitis; nr-axSpA, BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50%; nr-axSpA, non-radiographic axial spondyloarthritis.

Patients who initially respond to treatment are assumed to discontinue at a constant annual rate. Discontinuation probabilities for each of nr-axSpA and AS are presented in Table 32, and are aligned with those considered most appropriate by the committees in previous appraisals (54, 55, 122, 123). Discontinuation rates were assumed to be the same between bimekizumab, ixekizumab and secukinumab on the basis that efficacy and safety are similar (Section B.3.9 and Appendix D). This assumption is consistent with the assumption proposed by the external assessment group in TA383 (118). A similar assumption was made and accepted by the committee in the following NICE appraisals: TA407 (123), TA718 (54), TA719 (76), and TA829 (55).

Table 32: Annual discontinuation probabilities

Population	Annual discontinuation probability†	Rationale
Nr-axSpA	5%	This discontinuation probability has been used previously in TA383 (122) and TA718 (54)
AS	11%	This discontinuation probability has been used previously in TA383 (122), TA718 (54) and TA829 , and was preferred by the ERG in TA407 (123)

† Previous appraisals have used the terms “probabilities” and “rates” interchangeably. The values for discontinuation are from Pfizer’s etanercept submission in TA383 (122), where exponential distributions were fit to responders at 12 weeks to provide constant annual probabilities of discontinuation in nr-axSpA and AS.
Abbreviations: AS, ankylosing spondylitis; ERG, Evidence Review Group; nr-axSpA, non-radiographic axial spondyloarthritis.

B.4.2.2 Intervention and comparator acquisition costs

Drug acquisition costs for bimekizumab, ixekizumab, secukinumab 150 mg and secukinumab 300 mg are presented in Table 33. List prices for all technologies are sourced from the British National Formulary (208-210). A simple discount patient access scheme (PAS) is available for bimekizumab and is used in the cost-comparison analysis. Confidential PAS discounts are also available for ixekizumab and secukinumab; however, as these discounts are not known, the list prices are used in the cost-comparison analysis. Loading doses are included for ixekizumab and secukinumab, resulting in higher costs for these comparators in the first year; a scenario is considered in which loading doses are not included for the 300 mg dose of secukinumab.

Table 33: Acquisition costs of intervention and comparator technologies

	Bimekizumab	Ixekizumab	Secukinumab (150 mg)	Secukinumab (300 mg)
Pharmaceutical formulation	160 mg solution for injection in a pre-filled pen or syringe	80 mg solution for injection in a pre-filled pen or syringe	150 mg solution for injection in a pre-filled pen or syringe	300 mg solution for injection in a pre-filled pen
(Anticipated) care setting	Secondary care/home care†			
Acquisition cost (excluding VAT)	List price of £2,443.00 for two 160 mg injections; £1,221.50 per 160 mg dose PAS price of [redacted] for two 160 mg injections; [redacted] per 160 mg dose	List price of £1,125.00 for one 80 mg injection‡	List price of £1,218.78 for two 150 mg injections; £609.39 per 150 mg dose‡	List price of £1,218.78 for one 300 mg injection‡
Method of administration	Subcutaneous injection			
Dose	160 mg	80 mg	150 mg	300 mg
Dosing frequency	160 mg every 4 weeks	Initially 160 mg for 1 dose, then maintenance 80 mg every 4 weeks	150 mg every week for 5 doses, then maintenance 150 mg every month	300 mg every week for 5 doses, then maintenance 300 mg every month

†An initial training session with a nurse is required for each patient, after which all treatments are administered at home.
‡Ixekizumab and secukinumab are recommended by NICE subject to confidential patient access schemes that provide a discount on the list price. As these discounts are confidential, they cannot be included in the analysis and therefore ixekizumab and secukinumab are modelled at list price.
¶Secukinumab 300 mg is included as a comparator in both the AS and nr-axSpA populations, given that this dose is used in clinical practice in both populations (Section B.1.1.1); a scenario is considered in which loading doses are not included for the 300 mg dose.
Abbreviations: AS, ankylosing spondylitis; NICE, National Institute for Health and Care Excellence; nr-axSpA, non-radiographic axial spondyloarthritis; PAS, patient access scheme; VAT, value added tax.

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

Given that bimekizumab, ixekizumab, secukinumab 150 mg and secukinumab 300 mg are associated with similar efficacy and safety, the administration costs are the same, and no additional monitoring is required, healthcare resource use is expected to be the same between the considered technologies.

B.4.2.4 Adverse reaction unit costs and resource use

AEs are not included in the cost-comparison analysis as the safety profiles of bimekizumab, ixekizumab and secukinumab are similar based on the NMA (Section B.3.9 and Appendix D).

B.4.2.5 Miscellaneous unit costs and resource use

No additional cost types are included in the cost-comparison analysis, other than drug acquisition costs (Section B.4.2.2).

B.4.2.6 Clinical expert validation

Discontinuation probabilities have been aligned with those used in previous appraisals in nr-axSpA and AS (54, 55, 122, 123). No other elements of the cost-comparison analysis are expected to require clinical expert validation.

B.4.2.7 Uncertainties in the inputs and assumptions

A summary of model assumptions is presented in Table 34.

Table 34: Model assumptions

Assumption	Rationale
Bimekizumab, ixekizumab, secukinumab 150 mg and secukinumab 300 mg have equivalent efficacy and safety	See Section B.3.9 and Appendix D
The annual probability of discontinuation is the same for bimekizumab, ixekizumab, secukinumab 150 mg and secukinumab 300 mg	Efficacy and safety are similar for bimekizumab, ixekizumab, secukinumab 150 mg and secukinumab 300 mg (Section B.3.9 and Appendix D); discontinuation is therefore also expected to be similar. This approach was taken in previous appraisals in nr-axSpA and AS and considered appropriate by appraisal committees
Bimekizumab, ixekizumab, secukinumab 150 mg and secukinumab 300 mg have equivalent monitoring and administration	All treatments have the same administration costs, and no additional monitoring is required

Abbreviations: AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis.

B.4.3 Base-case results

Results of the cost-comparison analysis are presented in Table 35 and Table 36 for the nr-axSpA and AS populations, respectively. All considered technologies have confidential patient access schemes, however the PAS discounts for ixekizumab and secukinumab are unknown to UCB. Using the PAS price for bimekizumab and the list prices for the comparators, bimekizumab is associated with cost savings compared with ixekizumab and secukinumab 300 mg. Bimekizumab is associated with increased costs compared to secukinumab 150 mg. Differences in results between nr-axSpA and AS are driven by discontinuation rates and the prices of the technologies.

Table 35: Base-case results assuming PAS price for bimekizumab and list price for ixekizumab and secukinumab (nr-axSpA)

Technology	Total costs	Incremental costs (versus comparator)
Bimekizumab	[redacted]	[redacted]
Ixekizumab		
Secukinumab 150 mg		
Secukinumab 300 mg		

Abbreviations: nr-axSpA, non-radiographic axial spondyloarthritis; PAS, patient access scheme.

Table 36: Base-case results assuming PAS price for bimekizumab and list price for ixekizumab and secukinumab (AS)

Technology	Total costs	Incremental costs (versus comparator)
Bimekizumab	[redacted]	[redacted]
Ixekizumab		
Secukinumab 150 mg		
Secukinumab 300 mg		

Abbreviations: AS, ankylosing spondylitis; PAS, patient access scheme.

B.4.4 Sensitivity and scenario analyses

Scenario analyses are conducted at PAS price for bimekizumab and list prices for ixekizumab and secukinumab. The results of scenario analyses versus ixekizumab, secukinumab 150 mg and secukinumab 300 mg are presented in Table 37, Table 38 and Table 39, respectively.

All considered scenario analyses produce conclusions in line with the base case, and in line with expectations.

Table 37: Results of scenario analyses assuming PAS price for bimekizumab and list price for ixekizumab

Scenario	Incremental costs (versus ixekizumab)	
	Nr-axSpA	AS
Base case	[redacted]	[redacted]
Time horizon: 1 year		
Time horizon: 2 years		
Time horizon: 5 years		
Discounting costs: 3.5%		
Ixekizumab 16-week response assessment		
ASAS40 response rate		
No loading dose for secukinumab 300 mg		

Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; nr-axSpA, non-radiographic axial spondyloarthritis.

Table 38: Results of scenario analyses assuming PAS price for bimekizumab and list price for secukinumab 150 mg

Scenario	Incremental costs (versus secukinumab 150 mg)	
	Nr-axSpA	AS
Base case	[redacted]	[redacted]
Time horizon: 1 year	[redacted]	[redacted]
Time horizon: 2 years	[redacted]	[redacted]
Time horizon: 5 years	[redacted]	[redacted]
Discounting costs: 3.5%	[redacted]	[redacted]
Ixekizumab 16-week response assessment	[redacted]	[redacted]
ASAS40 response rate	[redacted]	[redacted]
No loading dose for secukinumab 300 mg	[redacted]	[redacted]

Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; nr-axSpA, non-radiographic axial spondyloarthritis.

Table 39: Results of scenario analyses assuming PAS price for bimekizumab and list price for secukinumab 300 mg

Scenario	Incremental costs (versus secukinumab 300 mg)	
	Nr-axSpA	AS
Base case	[redacted]	[redacted]
Time horizon: 1 year	[redacted]	[redacted]
Time horizon: 2 years	[redacted]	[redacted]
Time horizon: 5 years	[redacted]	[redacted]
Discounting costs: 3.5%	[redacted]	[redacted]
Ixekizumab 16-week response assessment	[redacted]	[redacted]
ASAS40 response rate	[redacted]	[redacted]
No loading dose for secukinumab 300 mg	[redacted]	[redacted]

Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; nr-axSpA, non-radiographic axial spondyloarthritis.

B.4.5 Subgroup analysis

No relevant subgroups were identified for inclusion in the analysis.

B.4.6 Interpretation and conclusions of economic evidence

The aim of this analysis was to compare the costs associated with bimekizumab, ixekizumab and secukinumab in the treatment of nr-axSpA and AS.

Using the PAS price for bimekizumab and list prices for the comparators, bimekizumab is associated with either cost savings or similar costs when compared with ixekizumab and secukinumab for both the nr-axSpA and AS populations. For the nr-axSpA population, bimekizumab is associated with cost savings of [redacted] versus ixekizumab and [redacted] versus secukinumab 300 mg, and incremental costs of [redacted] compared with secukinumab 150 mg over a time horizon of 10 years. For the AS population, bimekizumab is associated with cost savings of [redacted] versus ixekizumab and [redacted] versus secukinumab 300 mg, and incremental costs of [redacted] compared with secukinumab 150 mg.

All considered scenario analyses result in bimekizumab either being cost-saving or having similar costs when compared with ixekizumab and secukinumab in both nr-axSpA and AS patients.

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Appendices

All appendices are provided as separate documents.

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

Appendix D: Identification, selection, and synthesis of clinical evidence

Appendix E: Subgroup analyses

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: BE AGILE and BE AGILE 2 protocol and results

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Bimekizumab for treating active axial spondyloarthritis [ID6245]

Summary of Information for Patients (SIP)

May 2023

File name	Version	Contains confidential information	Date
ID6245_Bimekizumab_axSpA_CC_SIP	2.0	No	31st 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:

There are two patient populations being appraised by NICE: 1. Adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with signs of inflammation who have responded inadequately to or are intolerant of non-steroidal anti-inflammatory drugs (NSAIDs), 2. Adults with active ankylosing spondylitis (AS) who have responded inadequately to or who are intolerant of NSAIDs and physiotherapy.

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 (1). 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:

UCB supports the work of the National Ankylosing Spondyloarthritis Society (NASS). UCB is currently supporting NASS in three ways:

- Financial support for the Act on Axial SpA campaign. This campaign was instigated in 2020 and is a four-year commitment from UCB. Total campaign funding is approximately £800,000.
- Sponsorship of the Aspiring to Excellence programme. This is a quality improvement initiative led by NASS. UCB is one of a multi-company group sponsoring this initiative. Annual commitment is £30,000.
- Sponsorship of All Party Parliamentary Group (APPG) on Axial Spondyloarthritis. Alongside other pharmaceutical companies, UCB provides annual sponsorship of £16,500 to support the work of the APPG.

In 2022, UCB provided an unrestricted grant of £12,000 to ARMA to support a Best MSK implementation programme.

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.

AxSpA is an inflammatory arthritis that affects the spine and sacroiliac joints (joints that connect the bottom of the spine to the pelvis). AxSpA is a disease spectrum that contains both nr-axSpA; and AS, also known as radiographic axSpA (r-axSpA) (2). Patients with nr-axSpA and AS experience similar symptoms, disease burden, and are given similar treatments (2). In nr- axSpA, inflammation is visible by magnetic resonance imaging (MRI) or the patient has other symptoms, but there is no damage visible on X-rays. In AS, harmful bone fusion and growth can be seen on X-ray (3-5).

The underlying mechanisms of axSpA are thought to be inflammatory, with proinflammatory cytokines (a broad category of small proteins) playing a key role in the development of the disease. Specifically, a family of cytokines called interleukin (IL)-17 are thought to be the driving mechanism for radiographic damage (harmful bone growth and fusion) (6-9).

Raised levels of IL-17A and IL-17F are associated with chronic inflammation alongside other proinflammatory cytokines (10). IL-17A and IL-17F are also involved in the development of several other diseases, including psoriatic arthritis (PsA) and psoriasis (PSO), which have some overlapping clinical features with axSpA (11, 12).

Overall, axSpA is estimated to affect 1 in 200 (0.5%) patients in the UK (13). AS is more common in males (59–77% male), whereas nr-axSpA is more common in females (52–68% female) (5, 14, 15).

AxSpA is a painful disease, with key symptoms being chronic back pain, stiffness, and fatigue (16, 17). Straightforward daily tasks that many people take for granted are either not possible, or are painful or limited for people living with axSpA (18). These include routine household chores (such as gardening, ironing, hoovering) and daily necessities (getting dressed, tying shoelaces, getting out of bed, bathing and showering, and looking after children) (18). Patients are restricted in their ability to participate in sport, travel, take public transport, and drive a car (18). Many patients also experience peripheral manifestations (in joints other than the spine or sacroiliac joints), the most common of which are arthritis (affecting an estimated 18–58% of patients) and enthesitis (inflammation where a tendon or ligament attaches to bone, affecting 37–74% of patients) (19-21). AxSpA also leads to other

painful and disruptive conditions, including uveitis (inflammation of the eye), psoriasis (flaky skin), and inflammatory bowel disease (IBD) (17, 22-24). These conditions negatively affect patients' quality of life (25, 26), and often also result in fatigue, distress, depression, and anxiety (27-30). People with axSpA report that their condition negatively impacts their ability to work in both physically demanding and more stationary jobs, with their ability to think and concentrate often affected (18).

Although currently available treatments (Section 2c) improve disease outcomes, evidence from clinical trials shows that around 50–65% of patients with axSpA do not achieve what clinicians consider a meaningful response within 16–24 weeks (31-33). As such, many patients are required to switch treatments.

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?

The diagnosis of axSpA is based upon a combination of symptoms, physical examination, blood tests, and imaging tests (X-ray and MRI) (34). Based on the results, a clinician can determine the probability of axSpA causing the symptoms (34). Some patients need to be observed for a number of months before a clinician can be confident of the diagnosis. Generally, an axSpA diagnosis should be considered if you have daily back pain for more than 3 months that starts before the age of 45 years, especially if this back pain is mainly present in the morning, wakes you up at night, and improves after exercise (34). However, there is currently an average delay of 8.5 years to diagnosis, primarily caused by misdiagnosis.

Blood tests — There are no blood tests that can definitively diagnose axSpA. However, testing for the presence of one type of the human leukocyte antigen (HLA) gene, HLA-B27, can be helpful (34). axSpA is less likely in people without HLA-B27 who are white and of European descent (34). Tests for proteins that are markers of inflammation in the body, include C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) tests are sometimes helpful but are not diagnostic for axSpA (34).

Imaging tests — Most people with axSpA develop characteristic changes in the sacroiliac joints. In AS, these changes can be seen on X-ray images (34).

Imaging tests such as MRI detect the disease earlier than X-rays. In nr-axSpA, inflammation in the sacroiliac joints may be present on MRI when the X-rays are negative (34). Imaging tests should always be interpreted in the context of the symptoms, physical examination, and blood tests.

There are no additional tests or investigations for the diagnosis of axSpA for treatment with 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 treatment pathway for patients with axSpA in the UK is summarised in Figure 1.

Treatments aim to delay the progression of the disease by reducing damage to the spine and joints (35). The initial treatment for axSpA is NSAIDs to control pain and stiffness, maintain mobility, and reduce inflammation (36). Treatment with NSAIDs alongside physiotherapy is referred to as 'conventional therapy' (35). In patients with axSpA who respond inadequately or are intolerant of NSAIDs, available therapies in England include three types of drugs that reduce inflammation: tumour necrosis factor alpha (TNF-α), IL-17A, and Janus kinase (JAK) inhibitors, collectively known as biologic and targeted synthetic disease modifying anti-rheumatic drugs (b/tsDMARDs) (6, 35, 37-41) (Figure 1).

The available treatments for axSpA at second-line or later are:

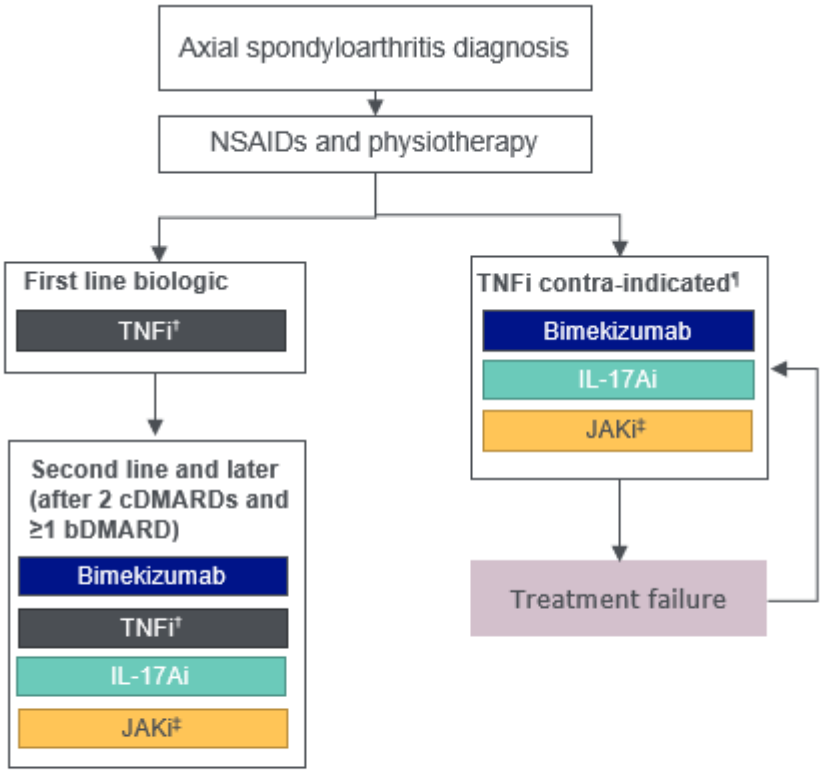
- IL-17A inhibitors (secukinumab, ixekizumab) target the proinflammatory IL-17 cytokine family, reducing the release of other inflammatory proteins associated with inflammation and harmful bone formation (42-44)

- TNF-α inhibitors (adalimumab, etanercept, certolizumab pegol, golimumab, infliximab) target TNF-α to inhibit the downstream signalling pathways associated with inflammation and harmful bone formation (45).

- JAK inhibitors (upadacitinib) target the JAK cytokine family (specifically JAK1), inhibiting various proinflammatory cytokines such as IL-7 and IL-21 (46).

However, the choice of second-line and later therapy is not well defined in the UK, and is guided by patient preference, symptoms, and comorbidities (47). Following TNF-α inhibitor failure at first line, there are few safe and effective treatment options with distinct modes of action. Patients typically receive secukinumab or ixekizumab, both of which inhibit IL-17A (2, 6, 38, 40). There is a need for therapies with different mechanisms of action to enable greater treatment choices for patients who respond inadequately to other therapies. This is especially true for patients who cannot tolerate adverse effects associated with TNF-α inhibitors or who cannot take TNF-α inhibitors (48).

Figure 1: NICE treatment pathway for axSpA including proposed position of bimekizumab



†Includes adalimumab, etanercept, certolizumab pegol, golimumab, infliximab†
‡Only in ankylosing spondylitis
¶Contraindicated means that is a reason for a person to not receive a particular treatment or procedure because it may be harmful. For example, having a bleeding disorder is a contraindication for taking aspirin because treatment with aspirin may cause excess bleeding

Abbreviations: bDMARD, biologic disease modifying antirheumatic drug; cDMARD, conventional disease modifying antirheumatic drug; IL-17Ai, interleukin 17A inhibitor; JAKi, Janus kinase inhibitor; NICE, National Institute for Health and Care Excellence; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitor.

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.

Between December 2022 and March 2023, UCB conducted a patient survey in collaboration with NASS to gain further insights into the impact of axSpA on people's physical, emotional, work, and overall wellbeing, as well as the effect on those around them (18). A total of 463 quantitative interviews were conducted with UK patients living with axSpA.

This patient survey (18) showed that the average time from experiencing symptoms to receiving a diagnosis is 9.2 years, with females having a significantly longer wait than males (9.7 years versus 8.2 years, respectively), despite both females and males first seeking medical help at similar times after experiencing symptoms. Those who took a longer time (more than 10 years) to receive their diagnosis were more likely to report the length of time to diagnosis negatively impacted their emotional well being than those diagnosed more quickly (less than 1 year) (76% vs 54%, respectively). Furthermore, those who took a longer time to receive diagnosis experienced more joint stiffness (85% vs 67%), fatigue (85% vs 63%), lower back pain (84% vs 66%), neck pain (73% vs 60%), and joint pain (72% vs 60%) versus those diagnosed more quickly.

The patient survey (18) also showed that, on average patients experienced eight different symptoms in the past 6 months, with the most common being joint stiffness (74%), lower back pain (72%), and fatigue (72%). As a result of their axSpA, patients have physical limitations that impact their daily lives, including a reduced ability to do jobs around the house (59%), and problems with walking (52%). Over half of all patients struggled with daily activities such as simple outside and household chores (such as gardening, taking out the bins, or hoovering). Activities such as participating in exercise, standing for long periods of time or going on holiday are negatively impacted, with 84% of people restricted in participating in exercise, and 75% struggling to go on holiday. Over 80% of people with axSpA reported their condition negatively impacts their ability to work in both physically demanding (including bar work, or working in a shop) and more stationary jobs.

The majority of patients felt their current treatment provided partial relief, but many still experienced numerous symptoms, with 65% of patients experiencing seven or more different symptoms in the past 6 months (18).

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 axSpA, certain cytokines can become overactive resulting in inflammation in the joints, tendons, and ligaments. There are two key cytokines, termed IL-17A and IL-17F that have been shown to be increased and play an important role in the inflammation and harmful bone formation that occurs in axSpA (6-9). Other cytokines such as TNF-α, have also been shown be play a role in axSpA and treatments exist that target this.

Bimekizumab is a monoclonal antibody, a protein designed to attach to IL-17A, IL-17F and IL-17A/F. Bimekizumab is the first biologic treatment designed to selectively block both IL-17A and IL-17F cytokines (49).

Inhibition of IL-17F in addition to IL-17A may block inflammation more than inhibition of IL-17A alone. By attaching to these cytokines, bimekizumab prevents them from interacting with their receptors on their target cells. As a result, bimekizumab inhibits the release of proinflammatory cytokines and chemicals, which subsequently reduces inflammation and radiographic damage, and provides relief of the symptoms related to axSpA.

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.

Not applicable.

3c) Administration and dosing

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

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

The recommended bimekizumab dose for adult patients with axSpA is 160 mg every 4 weeks given as one subcutaneous (under the skin) injection.

The timing and mode of administration are similar to ixekizumab (160 mg by subcutaneous injection at week 0, then 80 mg by subcutaneous injection every 4 weeks), and secukinumab (150 mg by subcutaneous injection at weeks 0, 1, 2, 3 and 4, then 150 mg by subcutaneous injection every 4 weeks). The secukinumab dose may also be increased to 300 mg, which is given either as one 300 mg subcutaneous injection, or two 150 mg subcutaneous injections.

If there has been no improvement following 16 weeks of treatment, bimekizumab may be discontinued.

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 used to support the reimbursement of bimekizumab for the treatment of axSpA comes from two Phase 3 randomised controlled trials (RCTs); BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS).

- BE MOBILE 1 (NCT03928704) is a large (n=254), Phase 3, multicentre, randomised, double-blind, placebo-controlled trial estimated to finish in June 2023.
- BE MOBILE 2 (NCT03928743) is a large (n=332) Phase 3, multicentre, randomised, double-blind, placebo-controlled trial, completed in August 2022.

Patients could take part in BE MOBILE 1 if:

- They were over 18 years of age with active nr-axSpA
- Had at least 3 months inflammatory back pain, were under 45 years old when their symptoms started, and damage to the spine/sacroiliac joints was not visible on an X-ray
- They had not responded to or were intolerant of NSAIDs.

Patients could take part in BE MOBILE 2 if:

- They were over 18 years older with moderate to severe AS
- Had at least 3 months inflammatory back pain and were under 45 years old when their symptoms started
- They had not responded to or were intolerant of NSAIDs.

Both studies consisted of a 16-week double-blind period, where some patients received bimekizumab, and others received a placebo (and neither group knew which they were taking), followed by a 36-week period, where everyone took bimekizumab. The total study period was therefore 52-weeks (referred to as the overall treatment period).

A trial design summary for both BE MOBILE 1 and BE MOBILE 2 is presented in Table 1.

Table 1: Summary of BE MOBILE 1 and BE MOBILE 2 trial design

Trial name	**BE MOBILE 1 (nr-axSpA) (50, 51)**	**BE MOBILE 2 (AS) (52, 53)**
Location	95 centres from 14 countries across North America, Western Europe, Eastern Europe, and Asia	
Randomisation	Treatment was grouped by region and by inflammation of the sacroiliac joint on MRI and elevated CRP: • MRI positive/CRP positive • MRI positive/CRP negative • MRI negative/CRP positive	Treatment was grouped by region and by previous use of TNF-α inhibitors
Blinding (for definition, see Glossary	Patients and site personnel were blinded to the treatment until study completion	
Study drugs	• Bimekizumab 160 mg/ml Q4W • Placebo Q4W	

Abbreviations: AS, ankylosing spondylitis; CRP, C-reactive protein; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, nonsteroidal anti-inflammatory drug; Q4W, every 4 weeks; TNF-α, tumour necrosis factor alpha.

In addition to BE MOBILE 1 and BE MOBILE 2, two further trials provide supportive long-term evidence for bimekizumab in AS (BE AGILE and BE AGILE 2).

The BE AGILE study (NCT02963506) was a 48-week randomised, parallel-group, Phase 2b, dose-ranging study, in patients with active AS. BE AGILE was conducted at 74 sites across

10 countries in Europe and the US. Patients who completed 48 weeks of treatment were eligible to enrol in the extension study (BE AGILE 2; NCT03355573) for an additional 204 weeks of treatment, with a subsequent safety visit 20 weeks after the last dose.

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 MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS) demonstrated that the dual inhibition of IL-17A and IL-17F with bimekizumab results in significant and rapid improvements in efficacy outcomes vs placebo (50, 51, 53) (Document B Section B.3.1).

Both BE MOBILE 1 and BE MOBILE 2 met their primary endpoints, with bimekizumab demonstrating a significant increase in the amount patients achieving Assessment of SpondyloArthritis International Society 40% (ASAS40) response across the disease spectrum at Week 16 vs placebo (51, 53, 54) (Document B Section B.3.6.1). ASAS40 is used in clinical trials for patients with axSpA, and measures disease activity, physical function, total spine pain, and spine stiffness. In order to achieve ASAS40, at least three of the four areas above need to improve by at least 40% and ≥2 units improvement, and the remaining area should be no more than 20% worse.

- BE MOBILE 1 (nr-axSpA): 47.7% vs 21.4%; odds ratio (OR): 3.51; p<0.001, bimekizumab vs placebo, respectively
- BE MOBILE 2 (AS): 44.8% vs 22.5%; OR: 2.88; p<0.001, bimekizumab vs placebo, respectively.

ASAS40 is an important outcome for patients, as the four areas it measures (disease activity, physical function, total spine pain, and spine stiffness) were highlighted as key areas of concern in the patient-based research discussed in Section 2d. Patients informed UCB/NASS that fatigue, lower back and neck pain, and spinal fusion were the top symptoms they wished they could make disappear, with one patients in the qualitive focus group saying: "*Lower back pain and the stiffness is the obvious symptom that never leaves - that's 24/7. The stiffness of*

back just never leaves my side so to speak, it's just always there and then the other symptoms, they just come and go depending on how my day is".

Importantly, the primary endpoint was met regardless of prior TNF-α inhibitor treatment (54). This is important as TNF-α inhibitors are often the first biologic treatment choice in axSpA. Patients who do not respond adequately to TNF-α inhibitors switch treatments; however in some cases, taking TNF-α inhibitors first means that the next treatment does not work as well as if TNF-α inhibitors had not been used first. In the BE MOBILE 1 and BE MOBILE 2 trials, bimekizumab shows similar results in patients who have not had TNF-α inhibitors and in patients who had previously had TNF-α inhibitors.

In both nr-axSpA and AS, bimekizumab also demonstrated statistically significant improvements vs placebo in all key secondary efficacy endpoints relating to disease activity, physical function, pain, and quality of life at Week 16 (Document B Section B.3.6.2.1).

Long-term (52-week) data from BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS) demonstrated that the response to bimekizumab treatment was maintained efficacy endpoints relating to disease activity, physical function, pain, and quality of life (Document B Section B.3.6.2.2).

A limitation of the BE MOBILE 1 and BE MOBILE 2 trials is they compared bimekizumab against a placebo, not another treatment. However, this is typical of the disease area and RCTs for other treatments.

This submission is a cost-comparison of bimekizumab vs ixekizumab. Whilst direct comparisons between bimekizumab and ixekizumab cannot be made using data from BE MOBILE 1 and BE MOBILE 2, evidence is provided by two network meta-analyses (NMAs) (reported in Document B Section B.3.9). NMA is a statistical method used to compare the effectiveness of multiple treatments by combining data from multiple studies. It allows for the estimation of treatment effects and ranking of treatments based on their effectiveness, even if no direct comparison has been made. This method provides a more comprehensive understanding of the relative effectiveness of different treatments for a particular condition.

Bimekizumab was associated with significantly improved change from baseline vs ixekizumab (the key comparator for this appraisal) in predominantly treatment-naïve patients with nr-axSpA in two key endpoints; Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI). BASDAI measures the activity of the disease based on your answers to six questions related to fatigue, spinal pain, peripheral joint pain/swelling, areas of localised tenderness, and duration and severity of morning stiffness, with a higher BASDAI score reflecting higher disease activity. BASFI is made up of 10 questions that are related to activities of daily living and are scored with a rating scale from 0 (no functional impairments) to 10 (maximal impairment). In no comparisons was bimekizumab statistically significantly worse than ixekizumab or secukinumab.

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 BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS) trials, quality of life was assessed using the Ankylosing Spondylitis Quality of Life (ASQoL) measure. The ASQoL scale was developed to assess the impact of interventions for AS on quality of life, and is an 18-item measure allowing calculation of a total score ranging from 0 to 18 (55). There is no such measure designed specifically for use in patients with nr-axSpA, but the ASQoL is routinely used in interventional clinical trials for patients with nr-axSpA (55).

In both nr-axSpA and AS, ASQoL significantly decreased (indicating improvement) with bimekizumab from baseline to Week 16 compared with placebo, and further decreased to Week 52.

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.

Phase 3 BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS) trials demonstrated that bimekizumab was well tolerated in the double-blind period vs placebo (16 weeks) and in the overall treatment period (52 weeks), consistent with early phase trials of bimekizumab in these patient populations (51, 53, 54, 56). The most commonly reported adverse events (AEs) with bimekizumab in patients with nr-axSpA (BE MOBILE 1) and AS (BE MOBILE 2) were a cold, upper respiratory tract infection, and oral candidiasis (a fungal infection of the mouth)

(Document B Section B.3.10.1). The incidence of serious adverse events and AEs leading to study discontinuation were low in both trials, and the risk of experiencing an AE did not increase with longer exposure to bimekizumab (Document B, Section B.3.10.1)

The phase 2 BE AGILE and BE AGILE 2 trials in AS demonstrated that the favourable safety profile of bimekizumab was maintained over 156 weeks (Document B, Section B.3.10.2).

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 Phase 3 trial programme of bimekizumab met its primary endpoint (ASAS40 at Week 16), and also reported significant improvements in additional ASAS responses, disease activity, physical function, pain, quality of life, and spinal mobility compared with placebo in patients with nr-axSpA and AS (51, 53, 54).

Additionally, more patients receiving bimekizumab achieved Ankylosing Spondylitis Disease Activity Score-major improvement (ASDAS-MI) than with placebo. ASDAS combines questions about back pain, peripheral pain/swelling, duration of morning stiffness, with another measure called the “patient global assessment of disease activity”. ASDAS-MI is a stringent clinical endpoint, and to achieve ASDAS-MI, a patient needs to improve by over 2.0 on a scale of 0 to infinity. This demonstrates that bimekizumab can lead to a large proportion of patients meeting stringent and clinically relevant treatment targets (57).

The BE MOBILE trials also provide evidence for bimekizumab working in patients with axSpA regardless of prior TNF-α inhibitor treatment. This is important as TNF-α inhibitors are often the first biologic medicine used to treat axSpA. Patients who do not respond adequately to TNF-α inhibitors switch treatments; however in some cases, taking TNF-α inhibitors first means that the next treatment does not work as well as if TNF-α inhibitors had not been used first. In the BE MOBILE 1 and BE MOBILE 2 trials, bimekizumab shows similar results in patients who have not had TNF-α inhibitors and in patients who had previously had TNF-α inhibitors.

Importantly, treatment responses were sustained until Week 52 while maintaining a favourable safety profile, and no new or unexpected safety concerns were observed.

Although direct comparisons between bimekizumab and ixekizumab cannot be made using data from BE MOBILE 1 and BE MOBILE 2, evidence for the efficacy of bimekizumab is supported by two NMAs (reported in Document B Section B.3.9). Bimekizumab was

associated with significantly improved change from baseline vs ixekizumab in predominantly treatment-naïve patients with nr-axSpA in two key endpoints; BASDAI and BASFI. In no comparisons was bimekizumab statistically significantly worse than ixekizumab or secukinumab.

The dual inhibition of IL-17F in addition to IL-17A with bimekizumab may therefore offer a promising treatment option for patients with axSpA, providing similar or improved disease outcomes vs ixekizumab. This provides clinicians with another therapy option in axSpA, helping 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 axSpA are also delivered by injection, and hence bimekizumab's method of administration is unlikely to increase the burden on patients compared with that of currently available treatments.

As with all treatments, there can be side-effects. Side-effects that patients taking this new drug might experience are listed above in Section 3g.

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 compares bimekizumab with ixekizumab, secukinumab 150 mg, and secukinumab 300 mg in axSpA

The model compares bimekizumab with ixekizumab, secukinumab 150 mg, and secukinumab 300 mg. Bimekizumab, ixekizumab, secukinumab 150 mg, and secukinumab 300 mg are assumed to have equivalent efficacy. Therefore, the model does not consider extension to life or differences in quality of life between the treatments. Only costs differ between treatments and are modelled. The only cost type that is expected to differ is drug acquisition costs.

At the start of the model, all patients are on treatment. At 16 weeks for bimekizumab and secukinumab (150 mg and 300 mg), and 16–20 weeks for ixekizumab, patients who do not achieve BASDAI50 ('non-responders') are assumed to discontinue treatment. Different proportions of patients achieving BASDAI50 are modelled for each of AS and nr-axSpA. Responders are assumed to discontinue at a constant annual rate. The costs of drug acquisition are only applied to those who have not discontinued.

In the model, drug costs differ between bimekizumab, ixekizumab and secukinumab (150 mg and 300 mg); however, the true difference is not known as all considered treatments have a confidential discount applied, known as a Patient Access Scheme. All other costs (including administration, monitoring, healthcare contacts and adverse event costs) are assumed to be the same between the treatments.

Uncertainty

A key assumption is that bimekizumab, ixekizumab and secukinumab (150 mg and 300 mg) have equivalent efficacy and discontinuation. It is also assumed that bimekizumab, ixekizumab and secukinumab (150 mg and 300 mg) have equivalent administration, monitoring, healthcare contacts, and adverse event costs.

Cost-effectiveness results

Bimekizumab, ixekizumab, and secukinumab have confidential discounts applied in the NHS. When publicly available list prices are used, bimekizumab is associated with similar costs to ixekizumab and secukinumab 300 mg, and increased costs compared with secukinumab 150 mg. When the confidential price for bimekizumab is compared to the list prices of

ixekizumab and secukinumab, bimekizumab is cost saving compared with ixekizumab and secukinumab 300 mg, and associated with similar costs compared with secukinumab 150 mg.

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)

Treatments currently recommended by NICE for axSpA include ixekizumab and secukinumab, which both target IL-17A. Bimekizumab targets both IL-17A and IL-17F, which is anticipated to result in greater reductions in inflammation than inhibition of IL-17A alone.

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

In 2021, the Department of Health and Social Care highlighted the need to improve women's health outcomes (58), with the Women's Health Strategy for England published in August 2022 (59). In this policy paper, the Department of Health and Social Care state that they are "addressing both the prevalence and disparities in musculoskeletal (MSK) conditions such as osteoarthritis, back pain, inflammatory arthritis and osteoporosis" (59). As nr-axSpA is more common in females than males (52–68% female) (5, 14, 15), (with females also typically experiencing a worse response to treatment with TNF-α inhibitors than males) (60), the addition of bimekizumab to the pathway could therefore help address the treatment gap that currently exists (59).

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 National Axial Spondyloarthritis Society (NASS): https://nass.co.uk/

2. Efficacy and safety results (up to Week 24) of BE MOBILE 1 and BE MOBILE 2 clinical trials https://ard.bmj.com/content/82/4/515

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

Adverse event: An unfavourable and unintended observation that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe.

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.

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

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.

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

Proinflammatory: Capable of causing inflammation

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.

4c) References

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Bimekizumab for treating axial spondyloarthritis [ID6245]

Clarification questions

June 2023

File name	Version	Contains confidential information	Date
ID6245 Bimekizumab EAG clarification questions response	1	Yes (CiC and AiC)	05/07/2023

Section A: Clarification on effectiveness data

NOTE: The EAG only had access to some of the documents very close to the submission deadline for these questions (due to corrupted files that had to be re-sent). It is possible that some of the questions are answered in these documents. If that is the case, please respond by pointing us to the correct document, including a page/table/figure number if possible.

Chosen comparator intervention

A1. PRIORITY: Clinical advice to the EAG was that secukinumab (SEC) 150mg is the most commonly used comparator and therefore is more likely to have the highest market share for non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS) patients. This is based on clinical experience of SEC 150mg being more efficacious than ixekizumab (IXE) in clinical practice, and the adverse injection site reactions associated with IXE which can cause patients to discontinue the medication. Clinical advice was also that SEC 300mg was not widely used in clinical practice. Furthermore, the estimates of market share in the budget impact component of the cost-comparison model, suggest that [redacted]. Based on this, please comment further on the decision to propose IXE rather than SEC 150mg as the main comparator in this appraisal.

UCB consider ixekizumab to be the most relevant comparator:

- United Kingdom (UK) clinicians consulted during advisory boards (N=9) consider bimekizumab and ixekizumab to be similar in terms of efficacy and safety (1). This is supported by both bimekizumab and ixekizumab having a similar affinity for binding to interleukin (IL)-17A in vitro while secukinumab has a lower affinity (2, 3). The network meta-analysis (NMA) does not support the clinical advisor's conclusion above (Document B Section B.3.9 and Appendix D).
- Ixekizumab is the most similar treatment, in terms of efficacy and safety (NMA; Section B.3.9 and Appendix D), has the most similar administration schedule and most similar trial structures. Bimekizumab is therefore expected to provide similar health benefits vs ixekizumab at a lower cost (Document B Section B.3.12).

- In the COAST trials for ixekizumab (4), injection site reactions (ISR) were reported by 42 (12.8%) patients in COAST-V and 18 (6.4%) patients in COAST-W. Most were mild or moderate in severity; two were severe. One patient discontinued study drug due to an ISR. However, ixekizumab is now available as a citrate-free formulation (5), which, in healthy participants, was bioequivalent, associated with less injection site pain, and had no other notable differences in the safety profile compared with the original commercial formulation (6). The new citrate free formulation should increase ixekizumab uptake. Bimekizumab is also citrate-free (7).
- Treatments with lower market share and established market presence may be more easy to displace than established treatments with higher market share, such as secukinumab 150 mg.
- Given the clinical similarities of ixekizumab and bimekizumab and ixekizumab's market position (8), ixekizumab is the most likely treatment to be displaced by bimekizumab in axial spondyloarthritis (axSpA), as reflected in the submitted budget impact model.

Secukinumab 300 mg has a trend towards increasing use in the UK and internationally:

- UCB market research and real-world evidence (RWE) studies provide numerous data-points that contrast with the clinical advice provided to the EAG.
- Market research commissioned by UCB with 50 independent rheumatologists (43 based in England, 3 in Scotland, and 4 in Wales) treating 6,183 adult axSpA patients in the last 12 months showed that, in patients receiving secukinumab, the 300 mg dose is used in 25% of patients with nr-axSpA (off label dose) and 34% of patients with AS (9). An additional source of market research reports that, in the UK between 2021 and 2022, 29.2% of patients who received secukinumab received the 300 mg dose (10).
- These UK market research data are in line with international trends on the usage of the 300 mg secukinumab dose in axSpA. RWE from Spain, the United States (US) and Germany show that that there is substantial 300 mg secukinumab use across the axSpA disease spectrum.
    - In a Spanish RWE study, 14% of all axSpA secukinumab patients (including biologic and targeted synthetic disease-modifying antirheumatic drug [b/tsDMARD] naïve and experienced patients) start treatment on the 300 mg secukinumab dose; however, in b/tsDMARD experienced patients 20–23% of patients initiated secukinumab with a 300 mg dose (11). Dose increases to 300 mg among patients who started on 150 mg were common with 15% of b/tsDMARD naïve, 20% of second-line b/tsDMARD patients and 28% of subsequent line patients uptitrating to a 300 mg secukinumab dose (11).

- An US RWE study found that 19.8% of secukinumab axSpA patients started treatment on the 300 mg dose and 21.1% of patients on a maintenance dose received 300 mg with 13% of the maintenance patients escalating to a 300 mg dose from 150 mg (12).
- In Germany, RWE found that [redacted]% of secukinumab axSpA patients started treatment on the 300 mg dose, and [redacted]% of patients on a maintenance dose received the 300 mg dose (13, 14). Presence of plaque psoriasis or psoriatic arthritis in axSpA patients increased the likelihood of receiving secukinumab 300 mg (13, 14).

A2. PRIORITY: Please report the market share for IXE and SEC (150mg and 300 mg) in:

a) **AS for i) biologic/targeted synthetic disease modifying anti-rheumatic drug (b/tsDMARD) naïve and ii) b/tsDMARD experienced patients.**

b) **nr-axSpA for i) b/tsDMARD naïve and ii) b/tsDMARD experienced patients.**

The market share estimates should be presented as proportions of patients treated with each interleukin-(IL)-17 inhibitor in UK clinical practice out of those who are eligible for biologic treatment in each population (AS or nr-axSpA) and by prior b/tsDMARD exposure within that population (AS or nr-axSpA).

In general, the restrictions applied to ixekizumab in TA718 will apply to bimekizumab. Ixekizumab is not recommended in the full b/tsDMARD naïve population, it is only recommended to tumour necrosis factor contraindicated (TNF-CI) b/tsDMARD naïve patients (15). Secukinumab is not restricted in the naïve population for AS, so is not the most appropriate comparator in the naïve population in AS (16). For budget impact estimates, it is most appropriate to restrict the naïve population in line with the proportion of patients who are TNF-CI. UCB did not identify any epidemiological studies that provided the proportion of patients who were TNF-CI. Clinicians consulted informally by UCB in multiple countries estimated that the rate of TNF-CI was between 5 and 10%. In our model, UCB have estimated 7% of b/tsDMARD naïve patients would be TNF-CI. There is no market share data for this population, so we have provided estimates of this population using RxY market research data (8).

The market share data for the b/tsDMARD experienced population is provided in the RxY market research data (8). Market share data are not available for secukinumab 150 mg and 300 mg separately from this research.

The proportion of secukinumab patients receiving each of the 150 mg and 300 mg doses was collected in a patient caseload survey of 50 UK rheumatologists treating 6,183 axSpA patients in the last 12 months (9). In the survey, respondents indicated that the 300 mg dose represents 25% of secukinumab use in nr-axSpA, and 34% of secukinumab use in AS (9). UK estimates are in line with those from RWE from Spain, the US and Germany (11-13).

Clinical evidence on bimekizumab

A3. Clinically important active infections are listed in the company submission as contraindications for bimekizumab (BKZ). Inflammatory bowel disease (IBD) is listed as a contraindication for the use of BKZ in patients with moderate to severe plaque psoriasis. Is BKZ also expected to be contraindicated for patients with IBD in axial spondyloarthritis (axSpA)?

Bimekizumab has the same 'special warnings and precautions for use' in the Summary of Product Characteristics (SmPC) as the IL-17A inhibitors ixekizumab and secukinumab (5, 17). IL-17A inhibitors are not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, IL-17A inhibitors should be discontinued and appropriate medical management should be initiated (18).

A4. The company submission (CS) states that "treatment with bimekizumab was associated with a lower incidence of acute anterior uveitis compared with placebo… (Table 26)". However, table 26 does not provide data on extra-articular manifestations separately and we cannot find these in any appendices for the BE MOBILE trials. Please provide the number of patients by arm at baseline, 16 weeks and at 52 weeks (BKZ only), with

a) **active inflammatory bowel disease**

b) **anterior uveitis and**

c) **psoriasis**

Extra-articular manifestations are reported in Table 1. Notably, as reported in the SmPC (19), in pooled data from BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS), at Week 16, the proportion

of patients developing a uveitis event was lower with bimekizumab (0.6%) compared with placebo (4.6%). The incidence of uveitis remained low with long-term treatment with bimekizumab (1.2/100 patient-years in the pooled phase 2/3 studies) (20).

Table 1: BE MOBILE 1 and BE MOBILE 2 extra-articular manifestations (safety set)

	BE MOBILE 1 (nr-axSpA)		BE MOBILE 2 (AS)	
	Bimekizumab 160 mg Q4W n=128 n (%)	Placebo n=126 n (%)	Bimekizumab 160 mg Q4W n=221 n (%)	Placebo n=111 n (%)
IBD				
Baseline	3 (2.3)	1 (0.8)	3 (1.4)	1 (0.9)
Week 16	1 (0.8)	1 (0.5)	4 (1.8)	0
Week 52	3 (1.2)	–	8 (2.4)	–
Uveitis				
Baseline	19 (14.8)	21 (16.7)	33 (14.9)	24 (21.6)
Week 16	2 (1.6)	6 (4.8)	0	5 (4.5)
Week 52	3 (1.2)	–	7 (2.1)	
Psoriasis				
Baseline	9 (7.0)	7 (5.6)	16 (7.2)	10 (9.0)

Source: UCB data on file. BE MOBILE 1 52 week CSR (21); UCB data on file. BE MOBILE 2 52 week CSR (22)
Abbreviations: AS, ankylosing spondylitis; IBD, inflammatory bowel disease; nr-axSpA, non-radiographic axial spondyloarthritis; Q4W, every four weeks.

A5. Peripheral symptoms of dactylitis, enthesitis and peripheral arthritis are listed in the NICE scope, but only a rationale for not including outcomes for dactylitis in the company submission has been provided. However, we cannot locate results for outcomes relating to enthesitis and peripheral arthritis in the submission documents. Where data are available, please provide the number of patients with enthesitis and peripheral arthritis by arm, in the BE MOBILE 1 and BE MOBILE 2 trials at baseline, 16 weeks and at 52 weeks (for BKZ).

Peripheral symptoms at baseline are reported in Table 2. A summary of enthesitis-free state based on the Maastricht Ankylosing Spondylitis Enthesitis (MASES) index in the subgroup of patients with enthesitis at baseline is provided in Table 3. Dactylitis and peripheral arthritis were not collected past baseline in the BE MOBILE 1 or BE MOBILE 2 trials.

Table 2: BE MOBILE 1 and BE MOBILE 2 peripheral symptoms (safety set)

	BE MOBILE 1 (nr-axSpA)		BE MOBILE 2 (AS)	
	Bimekizumab 160 mg Q4W n=128 n (%)	Placebo n=126 n (%)	Bimekizumab 160 mg Q4W n=221 n (%)	Placebo n=111 n (%)
Dactylitis				
Baseline	14 (10.9)	10 (7.9)	12 (5.4)	6 (5.4)
Enthesitis				
Baseline	37 (28.9)	46 (36.5)	64 (29.0)	24 (21.6)
Peripheral arthritis				
Baseline	51 (39.8)	53 (42.1)	85 (38.5)	40 (36.0)

Source: UCB data on file. BE MOBILE 1 52 week CSR (21); UCB data on file. BE MOBILE 2 52 week CSR (22)
Abbreviations: AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis; Q4W, every four weeks.

Table 3: BE MOBILE 1 and BE MOBILE 2 enthesitis-free state based on the MASES by visit (safety set)

	BE MOBILE 1 (nr-axSpA)		BE MOBILE 2 (AS)	
	Bimekizumab 160 mg Q4W n=94 n (%)	Placebo n=92 n (%)	Bimekizumab 160 mg Q4W n=221 n (%)	Placebo n=111 n (%)
Week 16	48 (51.1)	22 (23.9)	68 (51.5)	22 (32.8)
Week 52	51 (54.3)	–	67 (50.8)	–

Source: UCB data on file. BE MOBILE 1 52 week CSR (21); UCB data on file. BE MOBILE 2 52 week CSR (22)
Abbreviations: AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis; Q4W, every four weeks.

Systematic Literature Review (clinical)

A6. The searches cannot be fully appraised by the EAG as several search strategies are missing from Appendix D. Please provide the search strategies:

- **for the original clinical SLR in May 2012**
- **for the 6 update searches of the May 2012 clinical SLR:**
    - **1st update October 2013**
    - **2nd update July 2014**
    - **3rd update January 2017**
    - **4th update April 2018**
    - **5th update April 2019**
    - **6th update October 2020**

Search strategies have been provided in Appendix 1.

A7. Please clarify if the search strategies for the 7th update in April 2022 are those provided in the appendix of the NMA reports:

- **'Bimekizumab for the treatment of ankylosing spondylitis: 2023 SLR and NMA update. Date of preparation: 28th April 2023 Version: 3.0 (Document 1 of 5)' included in reference pack 2 of the company submission**
- **'Bimekizumab for the treatment of non-radiographic axial spondyloarthritis: 2023 SLR and NMA update. Date of preparation: 28th April 2023 Version: 3.0 (Document 1 of 4)' provided to the EAG on 14th June 2023.**

Yes, provided in Appendix 1: April 2022 and January 2023 clinical SLR update appendices of each of the NMA reports (23, 24).

Network meta-analysis

A8. PRIORITY: Please provide electronic versions of the WinBUGS code including data inputs, initial values for all chains, total number of burn-in and sampled iterations (including any thinning lag if used) so that the network meta-analysis (NMA) models for the following outcomes can be re-run and checked by the EAG:

a) **BASDAI 50**
b) **mean change BASDAI (from baseline)**
c) **BASFI scores (long-term change over time)**
d) **ASAS 40**
e) **ASAS 20**
f) **Discontinuation due to any reason**
g) **Discontinuation due to adverse events (AEs)**
h) **Serious adverse events (SAEs)**

If wrap-around functions were used to run these models (e.g. in R) please provide all relevant code so that analyses can be reproduced.

Please see files provided, folder names are as specified in Table 4. All code was run using a script in WinBUGS. An example of the script is provided in the accompanying files for BASDAI 50 for the predominantly b/tsDMARD-naïve AS population. Efficacy analyses were run with 10,000 burn-in and 3 chains of 1,000 samples; safety analyses were run for 50,000 burn-in and 3 chains of 20,000 samples.

Table 4: WinBUGS folders provided

Folder name	**Description**
Efficacy data inputs\bDexp	Efficacy outcome data inputs for b/tsDMARD-experienced patient population
Efficacy data inputs\bDn1	Efficacy outcome data inputs for b/tsDMARD pure naïve population
Efficacy data inputs\bDn2	Efficacy outcome data inputs for predominantly b/tsDMARD-naïve population
Safety data inputs	Safety outcome data for pooled axSpA population
Models\Binomial	WinBUGS code for running dichotomous outcome analyses, e.g. BASDAI 50
Models\Normal	WinBUGS code for running continuous outcome analyses, e.g. change from baseline BASDAI

Abbreviations: axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; b/tsDMARD, biological/targeted synthetic disease modifying anti-rheumatic drug.

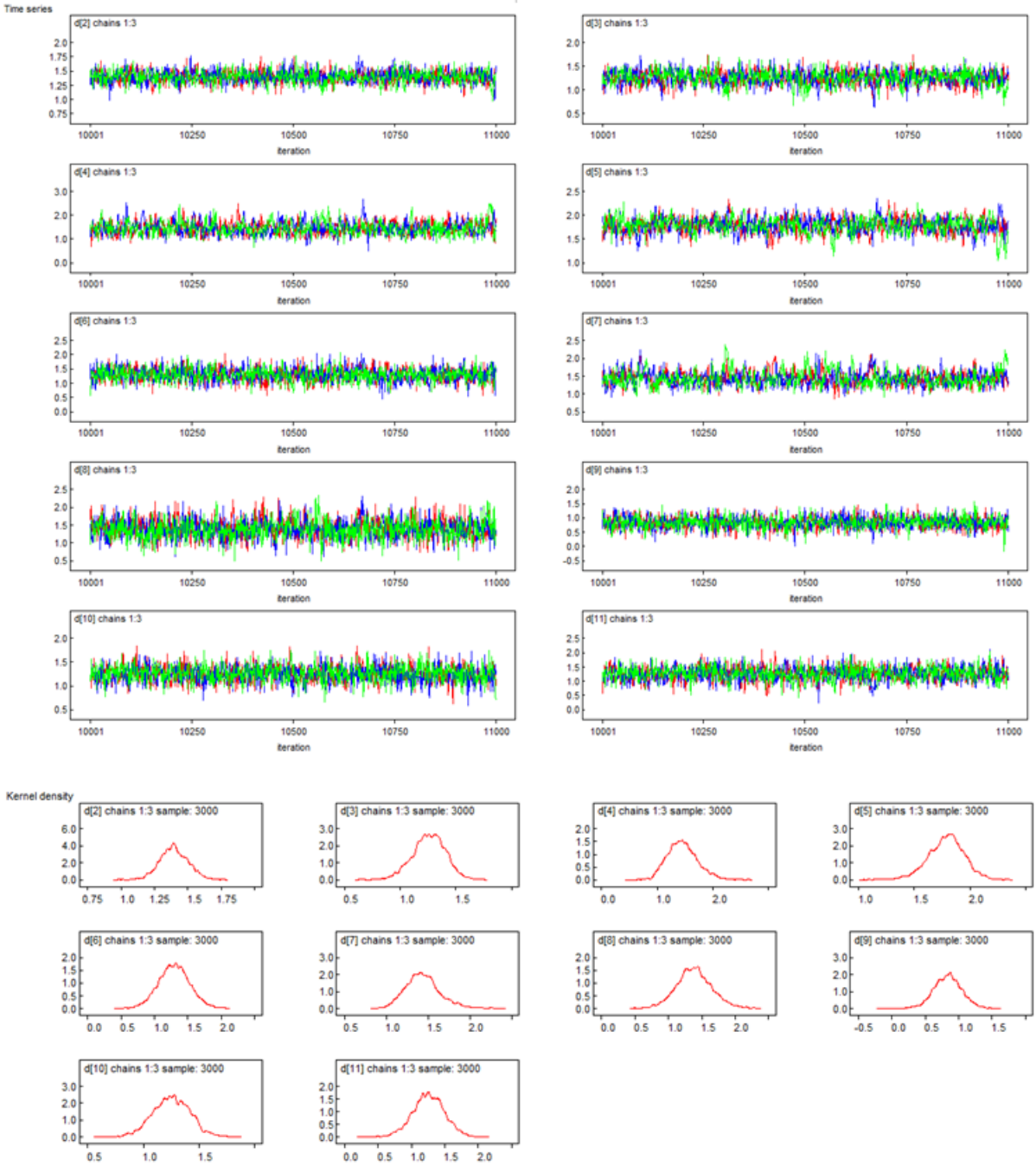
A9. PRIORITY: No details on convergence checks are provided, apart from a statement that *"For the efficacy outcomes. WinBUGs model was run for a minimum burn-in of 10,000 iterations to maximise convergence"* and *"…due to*

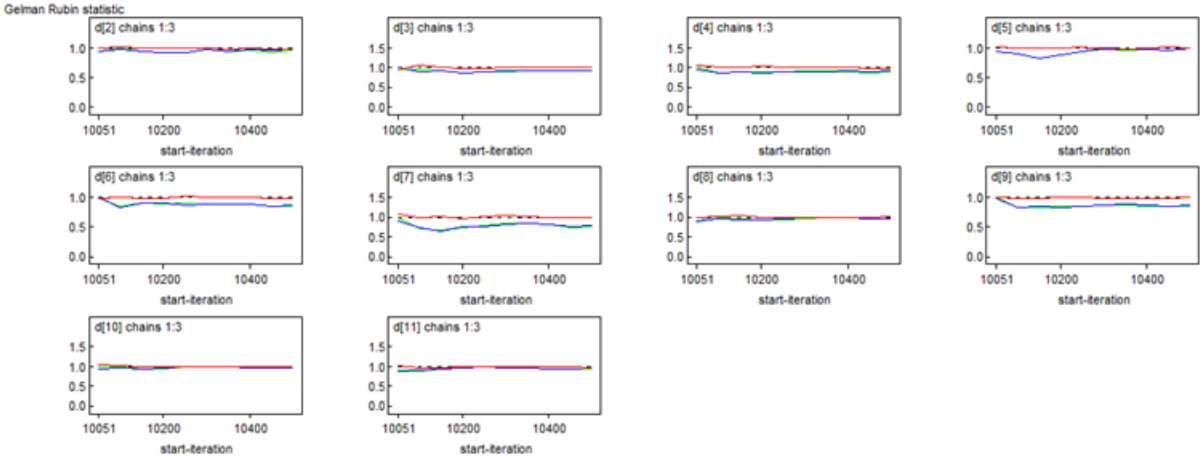
the small number of events across the safety outcomes, burn-in and subsequent chains were run longer for the safety analyses than for the efficacy analyses to maximise convergence, with the WinBUGs model run for a burn-in of 50,000 iterations" **(D.3.7.1, pages 87-88). As the required number of burn-in iterations can vary depending on the model and data, convergence of the Markov chain Monte Carlo (MCMC) chains needs to be checked for each model, before sampling from the posterior distributions.**

a) **Please provide details of the convergence checks performed (e.g. BGR plots, history plots) for each of the NMAs carried out for the outcomes in question A8.**

Convergence was confirmed by evaluation of the three chains and visual inspection of Brooks-Gelman-Rubin (BGR) plots. An example of the history, density and BGR trace plots for BASDAI 50 in the predominantly b/tsDMARD-naïve AS population are presented in Figure 1. The history plots show good overlap between the chains, there are no unexplainable spikes or abnormalities in the posterior density and the red line on the BGR plots approach 1.0 on the right hand side, therefore showing adequate convergence.

Figure 1: Trace plots, density plots, and Brooks-Rubin for BASDAI 50 in the b/tsDMARD-naïve AS population





Abbreviations: AS, ankylosing spondylitis; b/tsDMARD, biologic/targeted synthetic disease modifying anti-rheumatic drug; BASDAI 50, Bath Ankylosing Spondylitis Disease Activity Index 50% response.

b) If any models had not converged by 10,000 iterations (or 50,000 for safety), please ensure convergence and update results and model implementation description accordingly.

All models selected as best fit had converged by the 10,000 iterations burn-in for efficacy outcomes and 50,000 for safety outcomes. For safety outcomes, models were run using 50,000 burn-in as the default, as it was anticipated there may be some issues with convergence due to small number of events / zero events, especially in placebo treatment groups. Running random-effects (RE) models for safety outcomes with 200,000 burn-in did not improve model fit nor provide more clinically plausible relative treatment estimates, that would lead to an alternative decision on the most appropriate model for the data.

An update to the model fit table for discontinuation due to AE is provided (Table 5), this is provided to address the gaps identified by the company in the table previously submitted. Newly inserted values are shown in red.

Table 5: Corrected version of Table 147 of Appendix D: Model fit parameters: discontinuation due to AE

	Base models		PBO-adjusted models	
	Fixed effects	Random effects	Fixed effects	Random effects
Burn in	50,000	50,000	50,000	50,000
Number of chains	3	3	3	3
Samples per chain	20,000	20,000	20,000	20,000
Combined nr-axSpA and AS				
Datapoints	53	53	53	53
Total residual deviance	67.35	49.92	63.5	50.26
Posterior variance	37.12	54.92	36.83	51.71
DIC	206.341	197.307	189.398	176.847
Alt DIC	104.5	104.8	100.3	102.0
Between study standard deviation	NA	1.867 (0.5214, 4.27)	NA	1.331 (0.3137, 3.433)
Beta	NA	NA	0.986 (–0.808, 1.063)	0.9549 (–0.7902, 1.096)
Average residual deviance	1.271	0.942	1.200	0.948

Green highlight indicates chosen model. Red text indicates newly inserted values.
Abbreviations: AE, adverse event; AS, ankylosing spondylitis; DIC, Deviance Information Criterion; Alt DIC, Alternative Deviance Information Criterion estimate (= Total residual deviance + Posterior variance); NA, not applicable; nr-axSpA, non-radiographic spondyloarthritis; PBO, placebo.

A10. PRIORITY: It is stated that *"For the efficacy outcomes […] three chains of 1,000 samples were drawn from the posterior distributions"* and *"…for the safety analyses […] three chains of 20,000 samples drawn from the posterior distributions."* The number of required iterations to achieve a suitably large sample from the posterior distribution can vary depending on the model and data. This needs to be checked for each model, by inspection of the autocorrelation, chain mixing (e.g. in history plots) and by ensuring a large enough number of iterations are sampled such that the MC error is ≤5% of the standard deviation for key parameters (such as relative effects, regression coefficients and between-study heterogeneity). Please provide values for the MC error for all relative effect, heterogeneity and regression parameters (where applicable) for all NMA models fitted for the outcomes in question A8.

As described in the response to Question A9, model convergence was checked by inspection of the history, density and BGR trace plots. The MC error for relative effects, regression coefficients and between study heterogeneity for BASDAI50 in the predominantly b/tsDMARD-naïve AS population, for the fixed-effect (FE) placebo adjusted model are shown in Table 6. For the chosen model, the only key parameter with a MC error > 5% was or[1,4], which represented certolizumab pegol versus placebo, and had a MC error of 0.05489. Similar tables are available

in the log files (supplied separately) for all outcomes in Question A8, axSpA populations and networks.

Table 6: MC error for key parameters; AS, BASDAI50, predominantly b/tsDMARD-naïve network

Parameter	MC error for FE PBO adjusted model
or[1,2]	0.01266
or[1,3]	0.01849
or[1,4]	0.05489
or[1,5]	0.04679
or[1,6]	0.0223
or[1,7]	0.04071
or[1,8]	0.02967
or[1,9]	0.0119
or[1,10]	0.01261
or[1,11]	0.02454
or[2,1]	7.87E-04
or[2,3]	0.005262
or[2,4]	0.01465
or[2,5]	0.01334
or[2,6]	0.006606
or[2,7]	0.01141
or[2,8]	0.007942
or[2,9]	0.003266
or[2,10]	0.004127
or[2,11]	0.006136
or[3,1]	0.001708
or[3,2]	0.007966
or[3,4]	0.02187
or[3,5]	0.01849
or[3,6]	0.009819
or[3,7]	0.01839
or[3,8]	0.01369
or[3,9]	0.005581
or[3,10]	0.006241
or[3,11]	0.007063
or[4,1]	0.001981
or[4,2]	0.00907
or[4,3]	0.009363
or[4,5]	0.01481
or[4,6]	0.008165
or[4,7]	0.008237
or[4,8]	0.00831
or[4,9]	0.005036
or[4,10]	0.008092
or[4,11]	0.01103
or[5,1]	0.001073
or[5,2]	0.005073
or[5,3]	0.004866
or[5,4]	0.009593
or[5,6]	0.005757
or[5,7]	0.008249
or[5,8]	0.007155
or[5,9]	0.00334
or[5,10]	0.004079
or[5,11]	0.005231
or[6,1]	0.001498
or[6,2]	0.007349
or[6,3]	0.007645
or[6,4]	0.01451
or[6,5]	0.01588
or[6,7]	0.0118

Parameter	MC error for FE PBO adjusted model
or[6,8]	0.009403
or[6,9]	0.005162
or[6,10]	0.006726
or[6,11]	0.009813
or[7,1]	0.001929
or[7,2]	0.008714
or[7,3]	0.009798
or[7,4]	0.01003
or[7,5]	0.01496
or[7,6]	0.007527
or[7,8]	0.007522
or[7,9]	0.005247
or[7,10]	0.008273
or[7,11]	0.01119
or[8,1]	0.001819
or[8,2]	0.00819
or[8,3]	0.00935
or[8,4]	0.01272
or[8,5]	0.01634
or[8,6]	0.007184
or[8,7]	0.008853
or[8,9]	0.004891
or[8,10]	0.007709
or[8,11]	0.01083
or[9,1]	0.002225
or[9,2]	0.009997
or[9,3]	0.01117
or[9,4]	0.02641
or[9,5]	0.02871
or[9,6]	0.01395
or[9,7]	0.02144
or[9,8]	0.01593
or[9,10]	0.009014
or[9,11]	0.01348
or[10,1]	0.001068
or[10,2]	0.00563
or[10,3]	0.005553
or[10,4]	0.01702
or[10,5]	0.01553
or[10,6]	0.008543
or[10,7]	0.01501
or[10,8]	0.01083
or[10,9]	0.004159
or[10,11]	0.0069
or[11,1]	0.002305
or[11,2]	0.009177
or[11,3]	0.00736
or[11,4]	0.02424
or[11,5]	0.02641
or[11,6]	0.01237
or[11,7]	0.02083
or[11,8]	0.0166
or[11,9]	0.006435
or[11,10]	0.008002
beta	0.008956

Note: or[x, y] is the odds-ratio of y vs. x.
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; FE, fixed-effects; MC, Monte Carlo; NA, not applicable; or; odds ratio; PBO, placebo.

A11. PRIORITY: Details provided on the prior distributions used for the between-study heterogeneity are insufficient.

a) **Please provide details of the lower and upper bounds for the Uniform prior distribution used for the between-study heterogeneity for all random effects models fitted for the outcomes in question A8.**

As per the code provided with our response, the lower and upper bounds used in the RE models were uninformative priors as recommended in NICE DSU TSD2 (25) and TSD3 (26); see Table 7.

Table 7: NMA Model details

Outcome data type	Type of NMA model	Prior distribution for between-study heterogeneity
Binomial outcomes: count of patients with response/event	Binomial model with logit link	sd ~ dunif(0,2)
Binomial outcomes: count of patients with response/event	Binomial model with logit link With log odds of response in placebo arm as interaction term	sd ~ dunif(0,2)
Continuous outcomes: change from baseline	Normal model with identity link	sd ~ dunif(0.001,2)
Continuous outcomes: change from baseline	Normal model with identity link With change from baseline in placebo arm as interaction term	sd ~ dunif(0.001,2)

Abbreviations: dunif, uniform distribution; NMA, network meta-analysis; sd, standard deviation.

b) **Please justify the choice of upper bound for the Uniform distributions in a), taking into account the outcome scale, particularly for the continuous outcomes (see Section 6.2 of NICE DSU TSD2).**

For continuous outcomes, including mean change in BASDAI and BASFI scores from baseline, the uniform priors with upper bound of 2 were considered sufficiently uninformative.

A12. Several of the NMAs presented only have a maximum of 2 studies per comparison. Thus, there is not enough information to reliably estimate the between-study heterogeneity (a minimum of 5 studies per comparison is recommended for adequate estimation – see Gelman, 2006(27)). This results in posterior distributions for the between-study heterogeneity that are not updated from the prior due to lack of data for some NMA models.

a) **Please justify why RE models are considered for these networks.**

For completeness and transparency, we ran both FE and RE models, to allow a comparison of model fit to be made. FE models were used in these networks.

b) If there is *a priori* reason to believe that the included studies are likely to be heterogeneous but there is not enough information to reliably estimate the heterogeneity, the use of informative prior distributions for the between-study heterogeneity may be justified (Dias et al 2018,(28) sections 2.3.2 and 6.3.2; Röver et al 2021(29)). Please present results using an appropriate empirically informed or minimally informative prior distribution for the random effects models for each outcome considered in the NMAs.

Turner et al. 2019 (30) propose four approaches for specifying informative priors for multiple heterogeneity variances in a network meta-analysis. The efficacy and safety analyses presented have been re-run using the first approach, which is to assume that heterogeneity variances τ_{kl}^2 for all treatment comparisons in the network are equal. The empirical informed prior included for each outcome are reported in Table 8.

Table 8: Informative prior details

Outcome	General category chosen for outcome	Predictive prior for τ^2	Source of data-based predictive distribution
Change from baseline BASDAI	Signs/symptoms reflecting continuation/end of condition [a]	LN(-2.06,1.51^2)	Turner 2019 (30), Table S1
Change from baseline BASFI	Signs/symptoms reflecting continuation/end of condition [a]	LN(-2.06,1.51^2)	Turner 2019 (30), Table S1
BASDAI50	Signs/symptoms reflecting continuation/end of condition [a]	LN(-2.06,1.51^2)	Turner 2019 (30), Table S1
ASAS20	Signs/symptoms reflecting continuation/end of condition [a]	LN(-2.06,1.51^2)	Turner 2019 (30), Table S1
ASAS40	Signs/symptoms reflecting continuation/end of condition [a]	LN(-2.06,1.51^2)	Turner 2019 (30), Table S1
Discontinuation due to any reason	Withdrawals/dropouts	LN(-2.85, 1.60^2)	Turner 2019 (30)
Discontinuation due to AE	Withdrawals/dropouts	LN(-2.85, 1.60^2)	Turner 2019 (30)
SAE	Adverse event	LN(-1.97, 1.60^2)	Turner 2019 (30)

a, empirical priors for Pharmacological vs. Placebo/Control
Abbreviations: AE, adverse event; ASAS, Assessment in Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; LN, Log Normal; SAE, serious adverse event. τ^2, between study variance

As with the base cases, efficacy analyses were run for 10,000 burn-in and 3 chains of 1,000 samples; tolerability / safety analyses were run for 50,000 burn-in with 3 chains of 20,000 samples. The outputs for the comparisons between bimekizumab and the main comparators for the analyses are reported in Table 9 with results shown for the FE model and RE model with empirical priors. For the AS efficacy NMAs the models include placebo adjustment.

For the efficacy outcomes the results from the FE model and the corresponding RE model with empirically derived priors showed similar results. For most of the efficacy outcomes the Deviance Information Criterion (DIC) for the FE and RE models were similar (difference < 3) such that the DIC did not indicate that the RE model should be preferred over the FE model. The DIC for the RE model was higher than the FE model (difference > 3) for AS bDn1 and bDn2 BASFI and for AS bDn1 ASAS40. The FE model comparison for BKZ vs IXE was significantly different for nr-axSpA BASDAI (bDn1 and bDn2) and BASFI bDn2, but the corresponding RE model results were not significant. Placebo-adjusted models were not feasible for the nr-axSpA network, but where feasible this adjustment may be addressing some of the between study variance.

For discontinuation due to any reason, the model with the informative prior showed almost identical results to those for the FE model with the conclusion that there was no significant difference between bimekizumab and ixekizumab for this outcome. For discontinuation due to AEs, there was also an identical conclusion across models, showing no significant differences between the treatments. A slight reduction in DIC (~3 point reduction) was achieved in the informative prior model, as well a reduction in the total residual deviance. However, the 95% credible interval (CrI) was wide and standard deviation (SD) for the odds ratio (OR) estimate was large. In addition, for the informative prior model, several of the OR values estimated for low priority treatment contrasts from the global model, had mean OR estimates lying outside the 95% CrI, there were also some values of the SDs that were in the 10,000s and the upper limit of the 95% CrI across all the ORs ranged up to 2,171.

Therefore, there was no perceived benefit of choosing the informative prior model over the fixed-effect model for either of the safety outcomes.

Serious adverse events would not run without error with the informative prior for adverse events proposed by Turner 2019 (30). This analysis yielded a “cannot bracket slice for node” error for the informative prior, suggesting that the prior was too diffuse. Due to the need for a timely response, it was not possible to further investigate an alternative informative prior for this outcome.

Table 9: NMA treatment comparison of BKZ vs IXE fixed-effect or random-effect with empirical informative priors

Population and network	Outcome	Model	Median MD or OR (95% CrI)	Mean MD or OR (SD)	DIC	τ mean (SD)	Total residual deviance	Data points
Continuous outcomes, MD (95% CrI)								
nr-axSpA; bDn1	Change from baseline BASDAI	FE	-0.83 (-1.63, -0.02)	-0.83 (0.41)	12.38	NA	13.10	15
	Change from baseline BASDAI	RE inf prior	-0.84 (-2.18, 0.53)	-0.84 (0.68)	13.66	0.34 (0.11)	13.74	15
	Change from baseline BASFI	FE	-0.73 (-1.55, 0.11)	-0.73 (0.42)	10.45	NA	13.43	15
	Change from baseline BASFI	RE inf prior	-0.73 (-2.09, 0.69)	-0.74 (0.69)	12.21	0.35 (0.11)	14.18	15
nr-axSpA; bDn2	Change from baseline BASDAI	FE	-0.91 (-1.69, -0.09)	-0.91 (0.41)	17.65	NA	17.45	20
	Change from baseline BASDAI	RE inf prior	-0.87 (-2.16, 0.35)	-0.88 (0.63)	19.60	0.34 (0.11)	18.28	20
	Change from baseline BASFI	FE	-0.86 (-1.71, -0.08)	-0.87 (0.42)	18.79	NA	20.85	22
	Change from baseline BASFI	RE inf prior	-0.86 (-2.19, 0.48)	-0.88 (0.69)	20.43	0.35 (0.11)	21.14	22
AS; bDn1	Change from baseline BASDAI	FE PBO-ADJ	0.36 (-0.29, 1.04)	0.37 (0.34)	34.80	NA	37.06	38
	Change from baseline BASDAI	RE PBO-ADJ inf prior	0.38 (-0.55, 1.36)	0.39 (0.48)	37.90	0.28 (0.08)	35.17	38
	Change from baseline BASFI	FE PBO-ADJ	0.25 (-0.38, 0.85)	0.25 (0.32)	33.93	NA	37.46	41
	Change from baseline BASFI	RE PBO-ADJ inf prior	0.23 (-0.65, 1.09)	0.22 (0.44)	38.52	0.26 (0.08)	37.31	41
AS; bDn2	Change from baseline BASDAI	FE PBO-ADJ	0.19 (-0.29, 0.76)	0.20 (0.26)	35.69	NA	45.30	44
	Change from baseline BASDAI	RE PBO-ADJ inf prior	0.23 (-0.55, 0.94)	0.21 (0.39)	37.26	0.28 (0.07)	40.57	44

Population and network	Outcome	Model	Median MD or OR (95% CrI)	Mean MD or OR (SD)	DIC	τ mean (SD)	Total residual deviance	Data points
	Change from baseline BASFI	FE PBO-ADJ	-0.09 (-0.57, 0.39)	-0.09 (0.25)	35.84	NA	42.87	45
	Change from baseline BASFI	RE PBO-ADJ inf prior	-0.05 (-0.78, 0.70)	-0.05 (0.37)	40.00	0.27 (0.07)	41.66	45
Dichotomous outcomes, OR (95% CrI)								
nr-axSpA; bDn1	BASDAI50	FE	1.16 (0.45, 2.77)	1.27 (0.59)	119.31	NA	16.65	18
	BASDAI50	RE inf prior	1.11 (0.28, 4.57)	1.44 (1.48)	120.96	0.36 (0.11)	17.24	18
	ASAS 20	FE	1.76 (0.84, 3.86)	1.91 (0.81)	100.31	NA	13.87	15
	ASAS 20	RE inf prior	1.75 (0.53, 6.88)	2.22 (1.87)	101.22	0.34 (0.11)	14.08	15
	ASAS 40	FE	1.26 (0.54, 2.99)	1.41 (0.67)	132.35	NA	18.13	20
	ASAS 40	RE inf prior	1.30 (0.33, 5.24)	1.66 (1.72)	133.94	0.35 (0.12)	18.90	20
nr-axSpA; bDn2	BASDAI50	FE	1.17 (0.47, 2.97)	1.31 (0.65)	134.45	NA	18.14	20
	BASDAI50	RE inf prior	1.15 (0.29, 4.45)	1.45 (1.16)	136.37	0.34 (0.11)	19.06	20
	ASAS 20	FE	1.97 (0.89, 4.35)	2.14 (0.88)	150.14	NA	22.56	22
	ASAS 20	RE inf prior	1.91 (0.53, 7.31)	2.42 (2.10)	150.58	0.35 (0.11)	21.57	22
	ASAS 40	FE	1.46 (0.58, 3.52)	1.60 (0.74)	144.73	NA	21.11	22
	ASAS 40	RE inf prior	1.41 (0.36, 4.88)	1.72 (1.22)	145.66	0.35 (0.11)	21.06	22
AS; bDn1	BASDAI50	FE PBO-ADJ	0.95 (0.42, 1.75)	0.99 (0.35)	173.97	NA	30.81	27
	BASDAI50	RE PBO-ADJ inf prior	0.92 (0.33, 2.63)	1.06 (0.62)	172.95	0.33 (0.10)	26.73	27
	ASAS 20	FE PBO-ADJ	0.96 (0.48, 1.75)	1.00 (0.33)	288.51	NA	50.66	44
	ASAS 20	RE PBO-ADJ inf prior	0.96 (0.37, 2.48)	1.08 (0.56)	288.39	0.30 (0.07)	43.52	44
	ASAS 40	FE PBO-ADJ	0.99 (0.61, 1.52)	1.01 (0.24)	258.45	NA	41.72	42
	ASAS 40	RE PBO-ADJ inf prior	1.03 (0.50, 2.01)	1.09 (0.40)	262.22	0.25 (0.07)	38.60	42

Population and network	Outcome	Model	Median MD or OR (95% CrI)	Mean MD or OR (SD)	DIC	τ mean (SD)	Total residual deviance	Data points
AS; bDn2	BASDAI50	FE PBO-ADJ	0.88 (0.46, 1.59)	0.92 (0.30)	225.40	NA	38.31	35
	BASDAI50	RE PBO-ADJ inf prior	0.85 (0.33, 2.13)	0.95 (0.50)	224.83	0.31 (0.09)	33.86	35
	ASAS 20	FE PBO-ADJ	1.02 (0.62, 1.65)	1.05 (0.26)	333.22	NA	56.40	50
	ASAS 20	RE PBO-ADJ inf prior	1.01 (0.48, 2.09)	1.08 (0.43)	333.45	0.28 (0.07)	49.28	50
	ASAS 40	FE PBO-ADJ	0.99 (0.62, 1.50)	1.01 (0.23)	291.06	NA	47.67	46
	ASAS 40	RE PBO-ADJ inf prior	0.98 (0.50, 1.93)	1.04 (0.36)	293.26	0.25 (0.06)	43.02	46
Combined axSpA, all patients	Discontinuation due to any reason	FE	0.97 (0.33, 2.91)	1.14 (0.69)	262.727	NA	63.1	53
		RE Inf prior	1.04 (0.32, 3.66)	1.28 (0.96)	262.82	0.26 (0.17)	60.64	53
	Discontinuation due to AE	FE	0.65 (0.14, 3.13)	0.90 (0.89)	206.341	NA	67.35	53
		RE Inf prior	0.99 (0.14, 18.6)	5.51 (168.1)	203.012	0.65 (0.49)	59.69	53

Abbreviations: AE, adverse event; ASAS, Assessment in Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDn1, pure (b/tsDMARD) naïve network; bDn2 predominantly (b/tsDMARD) naïve network; BKZ, bimekizumab; CrI, credible interval; DIC, Deviance Information Criterion; FE, fixed effect; Inf prior, Informative prior; IXE, ixekizumab; MD, mean difference; PBO-ADJ, placebo adjusted; OR, odds ratio; RE, random-effects; SAE, serious adverse event; SD, standard deviation.

A13. The description of mean residual deviance as the "total residual deviance divided by number of data points" (D.3.7.1, page 88) is incorrect.

a) **Please clarify how the mean residual deviance was calculated for each of the NMAs carried out for the outcomes in question A8.**

Total residual deviance has been estimated using the standard calculation totresdev <- sum(resdev[]) from the WinBUGS code in NICE DSU TSD2 (25). For a well-fitting model, we would expect this number to be approximately the same as the number of independent datapoints in the model. To illustrate this further, we have calculated an "average" value by dividing the total residual deviance by the number of data points (described as "mean residual deviance" in our Methods summary). We would expect this value to be close to 1.0, as each data point should contribute approximately 1.0 to the posterior mean deviance.

b) **Please provide reference for the "alternative DIC" (D.3.7.1) from a peer reviewed publication.**

We have uploaded Gelman A. 2004. Bayesian data analysis, 2nd edition. Boca Raton, FL: Chapman & Hall/CRC. (Chapter 7). Available from http://www.stat.columbia.edu/~gelman/book/BDA3.pdf

A14. PRIORITY: The *posterior mean* of the residual deviance should be used to assess model fit. This should be calculated using the post-convergence iterations based on the appropriate formulas described in NICE DSU TSD2. Please provide the posterior mean of the residual deviance for each of the NMAs carried out for the outcomes in question A8, ensuring this is calculated using post-convergence iterations only.

This information is provided in the model fit tables, Supplement 1, 4 and 7 of Appendix D, as follows:

- Efficacy: nr-axSpA, Supplement 1, Tables 42-43.
- Efficacy: AS, Supplement 4, Tables 83-85.
- Safety: combined axSpA population, Supplement 7, Tables 146-148.

As an example, for AS outcomes in the predominantly b/tsDMARD-naïve network these are summarised in Table 10.

Table 10: Posterior mean of the residual deviance; AS, predominantly b/tsDMARD-naïve network

Outcome	Number of datapoints	Residual deviance for FE model	Residual deviance for RE model	Residual deviance for FE PBO adjusted model	Residual deviance for RE PBO adjusted model
BASDAI 50	35	37.26	35.37	38.31	36.08
Mean change in BASDAI	44	44.76	42.36	45.3	42.32
Mean change in BASFI	45	41.82	40.76	42.87	42.71
ASAS 40	46	51.74	46.70	47.67	44.77
ASAS 20	44	47.91	44.18	50.66	45.35

Abbreviations: ASAS, Assessment in Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; FE, fixed effect; PBO, placebo; RE, random effects.

A15. PRIORITY: Please provide more details on the assessment of consistency for the predominantly b/tsDMARD-naïve AS network.

a) In particular, please provide full details of the method used and point us to where the results are reported (document name, page/table/figure number).

An informal assessment of consistency between direct and indirect treatment effects was described in the company submission. One loop was identified across all efficacy populations in which inconsistency could potentially arise and this was in the pure b/tsDMARD-naïve and predominantly b/tsDMARD-naïve AS networks (Appendix D, Figure 38 and Figure 39). In both networks, this loop was formed of 3 treatment nodes: adalimumab, ixekizumab, and placebo, and the direct estimate of ixekizumab vs adalimumab from COAST-V was reviewed as it could potentially be inconsistent with the indirect estimate for the same comparison from the NMA. The assessment was done by reviewing the adalimumab vs placebo and ixekizumab vs placebo study level estimates (see the study-level forest plots in Supplement 6; Appendix D). These forest plots did not indicate any major heterogeneity in the study-level estimates and so it was considered reasonable to assume that the bimekizumab comparisons are not impacted by any inconsistency arising from the COAST-V adalimumab vs placebo estimates.

b) If possible, please also conduct a Bucher test (28, 31) to calculate a p-value for the agreement between direct and indirect evidence in this network.

Table 11 summarises the direct and indirect evidence in the pure b/tsDMARD-naïve and predominantly b/tsDMARD-naïve AS networks for the key outcomes listed in Question A8 for the loop adalimumab, ixekizumab and placebo. As an example, for BASDAI in the predominantly

b/tsDMARD-naïve AS network (bDn2), the indirect estimate for the relative effect of ixekizumab versus adalimumab was d_{ind} = –1.01 with variance, var_{ind} = 0.076. Comparing this with the direct estimate, d_{dir} = –0.50, we calculate an inconsistency estimate ω = –0.50 – (–1.01) = 0.51 with var_{ω} = 0.116 + 0.076 = 0.192. Then the z-value corresponding to the null hypothesis of no inconsistency is z-value = $0.51/\sqrt{0.192}$ = 1.166 with corresponding p-value = 0.878, indicating there is no evidence of inconsistency (p-value > 0.05). Similar methodology is followed for binary outcomes using ln(OR) and var = (standard error of ln(OR))^2. Across all estimates of the null hypothesis of no inconsistency, p-values were > 0.05. Therefore, there is no significant inconsistency in the loop adalimumab, ixekizumab and placebo across the key outcomes and populations.

Table 11: Assessment of inconsistency, summary of direct and indirect evidence with corresponding p-values for ixekizumab versus adalimumab

Endpoint	Network	Direct evidence: IXE vs. ADA	Indirect evidence: IXE vs. ADA	Estimate of null hypothesis of no inconsistency	p-value
MD (95% CI)					
BASDAI	AS; bDn2	–0.50 (–1.17, 0.17)	–1.01 (–1.55, –0.47)	1.166	0.878
	AS; bDn1	–0.50 (–1.17, 0.17)	–0.15 (–0.88, 0.59)	–0.698	0.485
BASFI	AS; bDn2	–0.30 (–0.95, 0.35)	0.19 (–0.35, 0.72)	–1.136	0.256
	AS; bDn1	–0.30 (–0.95, 0.35)	0.04 (–0.68, 0.75)	–0.683	0.495
OR (95% CI)					
BASDAI50	AS; bDn2	1.52 (0.81, 2.84)	0.88 (0.40, 1.95)	1.059	0.855
	AS; bDn1	1.52 (0.81, 2.84)	0.88 (0.40, 1.95)	1.059	0.855
ASAS20	AS; bDn2	1.25 (0.67, 2.32)	0.70 (0.41, 1.21)	1.371	0.915
	AS; bDn1	1.25 (0.67, 2.32)	0.71 (0.35, 1.41)	1.211	0.887
ASAS40	AS; bDn2	1.68 (0.91, 3.11)	1.12 (0.56, 2.20)	0.881	0.811
	AS; bDn1	1.68 (0.91, 3.11)	1.16 (0.58, 2.32)	0.786	0.784
Discontinuation due to any reason	Combined axSpA	1.58 (0.30, 8.23)	0.88 (0.29, 2.69)	0.571	0.716
Discontinuation due to AE	Combined axSpA	0.31 (0.01, 7.77)	1.83 (0.32, 10.27)	–0.949	0.343
SAE	Combined axSpA	0.47 (0.07, 3.23)	2.35 (0.37, 14.84)	–1.187	0.235

Abbreviations: ADA, adalimumab; AE, adverse event; AS, ankylosing spondylitis; ASAS, Assessment in Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDn1, pure b/tsDMARD-naïve network; bDn2, predominantly b/tsDMARD-naïve network; IXE, ixekizumab; MD, mean difference; OR, odds ratio; SAE, serious adverse event.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY: Please submit an updated version of the cost-comparison model with functionality to perform the additional sensitivity analyses requested throughout this section.

An updated version of the cost-comparison model has been provided in which the time point for response assessment is 16 weeks for all comparators (see Question B5). The results for this revised base case are presented in Table 12 and Table 13 for the nr-axSpA and AS populations, respectively.

Table 12: Results for revised base case (nr-axSpA)†

Technology	Total costs	Incremental costs (versus comparator)
Bimekizumab	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]

†Assuming PAS price for bimekizumab and list price for ixekizumab and secukinumab.
Abbreviations: nr-axSpA, non-radiographic axial spondyloarthritis; PAS, patient access scheme.

Table 13: Results for revised base case (AS)†

Technology	Total costs	Incremental costs (versus comparator)
Bimekizumab	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]

†Assuming PAS price for bimekizumab and list price for ixekizumab and secukinumab.
Abbreviations: AS, ankylosing spondylitis; PAS, patient access scheme.

The following options have also been included in the model:

- An option for the secukinumab 300 mg arm in which the 150 mg dose is used up to 16 weeks, and the 300 mg dose used thereafter (see Question B3)
- Additional options for the modelled response rate (see Question B4)
- An option for the time horizon to be set equal to the mean time on treatment (see Question B8).

Comparators

B2. PRIORITY: Please report the evidence sources and methodology used to inform the following Excel spreadsheets:

a) **"RxY. Data on file. CONFIDENTIAL. AxSpA market share analysis. 2022"(8)**

b) **"UCB. Data on file. CONFIDENTIAL. Therapy watch UCB cosentyx axSpA query 2023"(10)**

Descriptions of the methodology have been provided within the files supplied with this clarification.

B3. As mentioned in question A1, the EAG considers that SEC 300mg is not widely used in clinical practice, and therefore, is unlikely to be a relevant comparator. Furthermore, when SEC 300mg is used in AS, the British National Formulary(32) (BNF) suggests that it would be started at a 150mg up until clinical response assessment and only be escalated to 300mg after this. We note that the company submitted results of an online survey of UK rheumatologists, which suggests that [redacted] of nr-axSpA who are treated with SEC 300mg have previously received SEC 150mg.(9) The document does not contain corresponding information for the AS population. If the company wishes to retain the SEC 300mg comparison in the cost analysis, please update the treatment schedule in accordance with the posology described in the BNF for AS(32).

The cost-comparison model has been updated to include an option for the secukinumab 300 mg arm in which the 150 mg dose is used up to 16 weeks, and the 300 mg dose used thereafter. The results of this scenario analysis are presented in Table 14, and are broadly consistent with the revised base case.

Clinical experts at a UK advisory board stated that a proportion of patients would begin treatment on the 300 mg secukinumab dose, without trying the 150 mg dose first (1). This is also consistent with international RWE presented in Question A1. Therefore, both scenarios presented in Table 14 are relevant in the NHS.

Table 14: Results of scenario in which 150 mg secukinumab dose is used prior to 300 mg dose†

	Incremental costs (versus secukinumab 300 mg)	
	Nr-axSpA	AS
Revised base case	[redacted]	[redacted]
Scenario in which 150 mg secukinumab is used up to 16 weeks; 300 mg dose used thereafter		

†Assuming PAS price for bimekizumab and list price for secukinumab.
Abbreviations: AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis; PAS, patient access scheme.

Response rates

B4. PRIORITY: The response rates assumed by the company in the cost-comparison were sourced from the BKZ arm of the BE MOBILE 1 and BE MOBILE 2 trials for nr-axSpA and AS, respectively.

a) **Please justify the selection of data sources to inform these parameters. The EAG is particularly interested in understanding why the BKZ response rates in BE MOBILE 1 and BE MOBILE 2 were implicitly assumed to be more representative of the response rates for inhibitors of IL-17 (IL-17A alone or both IL-17A and IL-17F), given these could also have been informed by SEC or IXE trial data. Another alternative would have been to apply a pooled response rate for IXE, SEC 150 mg and BKZ across the relevant trials, which effectively assumes the same effectiveness for intervention and comparators and makes use of more evidence. Please comment on the suitability of these alternative approaches.**

b) **Given that response rates for IL-17 inhibitors (and other biologics) in AS and nr-axSpA are known to differ according to prior b/tsDMARD exposure (naïve vs. experienced), please justify why the response rates applied in the model were informed by results for the full population in the BE MOBILE 1 and BE MOBILE 2. Please comment how likely are the BE MOBILE 1 and BE MOBILE 2 populations to be reflective in terms of prior b/tsDMARD exposure of the AS and nr-axSpA UK populations, presenting evidence on the proportion of patients in clinical practice**

who have had prior b/tsDMARD exposure (by population: AS and nr-axSpA).

c) Please conduct further sensitivity analyses on the response rate parameters (particularly BASDAI50) by population considering:

i. Alternative sources of evidence (e.g., using trial data from SEC (150mg) and IXE trials, and/or using a pooled response rate for BKZ, SEC (150 mg) and IXE obtained by NMA);

ii. Response rate estimates by prior b/tsDMARD exposure (naïve vs. experienced) using the data sources mentioned in the previous point.

In line with the substantial overlap of efficacy data in the NMA results, the model assumes equivalent efficacy for all comparators. When all response rates are varied in the same direction and same magnitude for all comparators simultaneously, response rates are not typically a model driver. For simplicity, the overall values from BE MOBILE 1 and BE MOBILE 2 were used.

The company agrees with the EAG that data for secukinumab or ixekizumab could also be used to inform this parameter and present alternative BASDAI50 response rates in Table 15. Note that values have not been used from the NMA as an analysis was not conducted for the b/tsDMARD experienced population for nr-axSpA.

Table 15: Alternative BASDAI50 response rates

		Bimekizumab	Ixekizumab	Secukinumab
Nr-axSpA	b/tsDMARD-naïve	47.5%†	31.3%¶	39.0%‡‡
	b/tsDMARD-experienced	40.0%†	NA	NR
	Overall	46.9%†	NR	37.3%‡‡
AS	b/tsDMARD-naïve	48.9%‡	42.0%§	32.4%¶¶
	b/tsDMARD-experienced	35.1%‡	21.9%††	NR
	Overall	46.6%‡	NR	30.6%§§

Source: †BE MOBILE 2 (33); ‡BE MOBILE 2 (34); ¶ COAST-X (35); §COAST-V (36); ††COAST-W (37); ††PREVENT (38); ¶¶ ASTRUM (39); §§ MEASURE 2 (40).
Abbreviations: AS, ankylosing spondylitis; NA, not available; NR, not reported; nr-axSpA, non-radiographic axial spondyloarthritis.

Options have been included in the cost-comparison model to consider the highest and lowest response rates from those presented in Table 15. The results of these scenario analyses are presented in Table 16. Scenario results using the highest (47.5% for nr-axSpA and 48.9% for AS, respectively) and lowest (31.3% for nr-axSpA and 21.9% for AS, respectively) BASDAI50 response rates are broadly consistent with the revised base case.

Table 16: Results of scenarios using highest and lowest BASDAI50 response rates†

	Incremental costs (versus ixekizumab)		Incremental costs (versus secukinumab 150 mg)		Incremental costs (versus secukinumab 300 mg)	
	Nr-axSpA	AS	Nr-axSpA	AS	Nr-axSpA	AS
Revised base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario using highest response rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario using lowest response rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Assuming PAS price for bimekizumab and list prices for ixekizumab and secukinumab.
Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; nr-axSpA, non-radiographic axial spondyloarthritis; PAS, patient access scheme.

Time point for treatment response assessment

B5. PRIORITY: The company modelled a different time point for treatment response assessment for patients treated with IXE (at 16 weeks for 50% of patients and at 20 weeks for the remainder 50%) and those treated with SEC and BKZ (at 16 weeks).

a) **Please justify the proportions of patients assessed for response at 16 and 20 weeks, for those treated with IXE.**

b) **Since the model assumes that the proportion of patients who do not achieve BASDAI50 ('non-responders') discontinue treatment, the use of different time points for response assessment across treatments means that the proportion of patients on treatment will also vary across treatments. Given this, and in the context of a cost-comparison, costs of subsequent treatments for all comparisons would have to be modelled in order to appropriately capture any cost differences. The need to include subsequent treatments could also modify the definition of relevant time horizon, which should be long enough to reflect materially important differences between the technologies being compared. Please comment on this and consider assuming instead 16 weeks as the**

common time point for response assessment across all treatments in the cost-comparison.

In the absence of data on the proportion of patients assessed for response at each of 16 and 20 weeks, a distribution of 50% of patients assessed at each time point was assumed.

The cost-comparison model has been updated to assume that all patients are assessed for response at 16 weeks. The results for the revised base case are presented in Question B1.

Treatment discontinuation probabilities in the maintenance period

B6. PRIORITY: The cost-comparison assumes that patients in the maintenance period (i.e., after treatment response is assessed in the model) are exposed to a constant probability of treatment discontinuation, which varies by population (AS and nr-axSpA).

a) **Please comment if there is more contemporaneous evidence that could be used to inform treatment discontinuation probabilities in the maintenance period (conditional on obtaining treatment response at the end of the trial period) given that the evidence used to inform these parameters in TA383 (and subsequent appraisals) was collected in open-label trials largely conducted in the early 2000s. If you can identify more contemporaneous evidence on probabilities of treatment discontinuation in the maintenance period (conditional on initially achieving response), please present sensitivity analyses using these alternative estimates.**

b) **Treatment discontinuation probabilities in the maintenance period were assumed to be independent of prior b/tsDMARD exposure (naïve vs. experienced); please justify this assumption and comment on whether existing evidence (e.g., recent randomised clinical trials or registry data) supports this assumption.**

Available RWE on discontinuation rates is presented in Table 17. There is some evidence to suggest that discontinuation rates increase with line of therapy; however, there are no available data to support different rates of discontinuation between IL17 inhibitors. The same discontinuation rate was therefore assumed for bimekizumab, ixekizumab, and secukinumab.

Given that the discontinuation rate for secukinumab was found to be similar to that for TNF-α inhibitors, it was considered appropriate to use rates originally derived from data in patients receiving TNF-α inhibitors; these rates also align with previous HTA appraisals in nr-axSpA and AS (15, 16, 41, 42).

Table 17: Real-world evidence on discontinuation rates

Source	Key finding
Glintborg 2020 (43)	In patients with spondyloarthritis, secukinumab had a one-year retention rate comparable to adalimumab as first or second line biologic therapy, but a poorer retention rate compared with adalimumab as third+ line of biologic therapy
Min 2021 (44)	In patients with AS who had received a TNF-α inhibitor previously, drug discontinuation was comparable for patients receiving secukinumab and TNF-α inhibitors
Glintborg 2013 (45)	In patients with AS, discontinuation was higher in patients who had switched to a new biologic therapy compared with those receiving their first biologic therapy
Griffiths 2022 (46)	In patients with AS, median persistence on second and third-line biologic therapy was lower than for first-line therapy

Abbreviations: AS, ankylosing spondylitis; TNF-α, tumour necrosis factor alpha.

c) For patients treated with IXE, the company only applies the probability of treatment discontinuation after week 20, despite 50% of patients having response assessed at 16 weeks. Please correct the model and update the cost-comparison analysis so that the probability of treatment discontinuation for IXE is applied from i) week 20 onwards for patients who have treatment response assessed at 16 weeks, and ii) week 24 onwards for patients who have treatment response assessed at 20 weeks. Note that this update is not necessary if the company decides to update their cost-comparison analysis as suggested in question B5.b).

The cost-comparison model has been updated to assume that all patients are assessed for response at 16 weeks (see Question B5b).

Treatment schedule

B7. The company presents a scenario whereby it is assumed that SEC 300mg is administered without a loading dose (i.e., assuming 1 dose instead of 5 doses in the first model cycle). Please provide the rationale for this scenario, commenting whether this treatment schedule for SEC 300mg (i.e., without a loading dose) i) is likely to be observed in UK clinical practice and ii) whether there is effectiveness and safety evidence to support its use.

Two scenarios were considered for secukinumab 300 mg patients in the original submission:

- A 300 mg dose with no loading doses, designed to represent patients who have switched to the 300 mg dose following inadequate response to the 150 mg dose, in line with the SmPC for secukinumab (17)

- A 300 mg dose with 5 loading doses of 300 mg, designed to represent patients who are initiated on the 300 mg dose; note that this would reflect off-label use.

As discussed in response to Questions A1 and A2, it is considered that these two original scenarios and the scenario presented in Question B3 reflect the range of possible uses of the 300 mg dose of secukinumab.

Time horizon

B8. PRIORITY: The EAG considers that the most appropriate time horizon corresponds to the mean time on treatment (assuming that this is the same across all treatments; see question B5.b). Please justify your base-case assumption on the time horizon length and present a sensitivity analysis for a time horizon equal to mean treatment duration.

A 10-year time horizon was considered as a conservative base case as it minimises the effect of induction regimens for ixekizumab and secukinumab. As bimekizumab does not have an induction regimen in axSpA, a longer time horizon favours comparators.

An option has been included in the cost-comparison model for the time horizon to be set equal to the mean time on treatment (3.1 years). The results of this scenario analysis are presented in The results show that a larger proportion of the differences between comparators fall in the first 3.1 years of the model than in the final 6.9 years of the model.

Table 18. The results show that a larger proportion of the differences between comparators fall in the first 3.1 years of the model than in the final 6.9 years of the model.

Table 18: Results of scenario in which time horizon is equal to mean time on treatment

	Incremental costs (vs IXE)		Incremental costs (vs SEC 150 mg)		Incremental costs (vs SEC 300 mg)	
	Nr-axSpA	AS	Nr-axSpA	AS	Nr-axSpA	AS
Revised base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario in which time horizon is equal to mean time on treatment (3.1 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Assuming PAS price for bimekizumab and list prices for ixekizumab and secukinumab.
Abbreviations: AS, ankylosing spondylitis; IXE, ixekizumab; nr-axSpA, non-radiographic axial spondyloarthritis; SEC, secukinumab.

Section C: Textual clarification and additional points

General questions

C1. PRIORITY: Please provide the following clarifications on Table 16 (CS, pages 55-56)

a) **Column headings for the relative effects are labelled as "Odds ratio/ difference". However, it is not clear which measure is being reported in each case. For example, in the row labelled 'ASAS40 in TNF-α inhibitor-naïve patients, n (%)' it appears that the relative effect reported is an odds ratio for BE MOBILE 1, but a percentage difference for BE MOBILE 2 (if it is an odds ratio please check this value as OR=22.2 seems implausible). Please clarify which measure is being reported in each case, and be consistent for BE MOBILE 1 and 2.**

b) **In the row labelled 'ASAS40 in TNF-α inhibitor IR [NRI], n (%)¶' please check and correct the percentage given for the placebo arm of BE MOBILE 2 (current value displayed is 176)**

A. A corrected version of Table 16 is provided in Table 19. Difference from placebo is indicated by ‡. All between-group differences are adjusted risk differences (percentages) from the logistic regression model for binary endpoints or mean differences vs placebo from the ANCOVA model for continuous endpoints. The exception is ASAS40 in TNF-α inhibitor-naïve patients for BE MOBILE 1, which was not in the statistical testing hierarchy.

B. In the row labelled 'ASAS40 in TNF-α inhibitor IR [NRI], n (%)¶' the percentage given for the placebo arm of BE MOBILE 2 has been corrected to 17.6.

Table 19: Corrected version of Table 16: Summary of ranked secondary efficacy analysis results based on the predefined sequential testing sequence at Week 16 (randomised set)

	BE MOBILE 1 (nr-axSpA)					BE MOBILE 2 (AS)				
Endpoint	Bimekizumab 160 mg Q4W N=128	Placebo N=126	Odds ratio (95% CI)	Between group difference‡	p-value	Bimekizumab 160 mg Q4W N=221	Placebo N=111	Odds ratio (95% CI)	Between group difference	p-value
ASAS40 in TNF-α inhibitor-naïve patients, n (%)†	55 (46.6)	25 (22.9)	3.08† (1.71, 5.54)	–	0.0002	84 (45.7)	22 (23.4)	22.2‡ (10.6, 33.9)	–	<0.001
ASAS40 in TNF-α inhibitor IR [NRI], n (%)¶	6 (60.0)	2 (11.8)	–	–	–	15 (40.5)	3 (17.6)	–	–	–
BASDAI CfB [MI], mean (SE)	–3.1 (0.20)	–1.5 (0.2)	–	–1.5‡ (–2.0, –1.0)	<0.001	–2.9 (0.1)	–1.9 (0.2)	–	–1.0‡ (–1.5, –0.6)	<0.001
ASAS20 [NRI], n (%)	88 (68.8)	48 (38.1)	31.4 (19.5, 43.2)	–	<0.001	146 (66.1)	48 (43.2)	24.0 (12.8, 35.2)	–	<0.001
ASAS PR [NRI], n (%)	33 (25.8)	9 (7.1)	19.4 (10.1, 28.7)	–	<0.001	53 (24.0)	8 (7.2)	14.7 (7.3, 22.1)	–	<0.001
ASDAS-MI [NRI], n (%)	35 (27.3)	9 (7.1)	19.0 (10.7, 27.2)	–	<0.001	57 (25.8)	6 (5.4)	18.6 (10.9, 26.3)	–	<0.001
ASAS 5/6 [NRI], n (%)	58 (45.3)	26 (20.6)	25.7 (14.1, 37.3)	–	<0.001	109 (49.3)	21 (18.9)	29.3 (19.2, 39.3)	–	<0.001
BASFI CfB [MI], mean (SE)	–2.5 (0.2)	–1.0 (0.2)	–	–1.5‡ (–2.0, –1.0)	<0.001	–2.2 (0.1)	–1.1 (0.2)	–	–1.1‡ (–1.5, –0.6)	<0.001
NSP CfB [MI], mean (SE)	–3.6 (0.3)	–1.7 (0.2)	–	–1.8‡ (–2.4, –1.2)	<0.001	–3.3 (0.2)	–1.9 (0.2)	–	–1.5‡ (–2.0, –1.0)	<0.001
ASQoL CfB [MI], mean (SE)	–5.2 (0.4)	–2.5 (0.4)	–	–2.6‡ (–3.7, –1.6)	<0.001	–4.9 (0.3)	–3.2 (0.3)	–	–1.5‡ (–2.4, –0.7)	<0.001
SF-36 PCS CfB [MI], mean (SE)	9.5 (0.7)	5.5 (0.7)	–	4.0‡ (2.1, 5.8)	<0.001	9.3 (0.6)	5.9 (0.8)	–	3.4‡ (1.7, 5.1)	<0.001

	BE MOBILE 1 (nr-axSpA)					BE MOBILE 2 (AS)				
Endpoint	Bimekizumab 160 mg Q4W N=128	Placebo N=126	Odds ratio (95% CI)	Between group difference‡	p-value	Bimekizumab 160 mg Q4W N=221	Placebo N=111	Odds ratio (95% CI)	Between group difference	p-value
BASMI CfB [MI], mean (SE)§	–0.4 (0.1)	–0.1 (0.1)	–	–	–	–0.5 (0.1)	–0.2 (0.1)	–	–0.3‡ (–0.5, –0.1)	0.006

Source: Baraliakos, 2022a (47); Baraliakos, 2022b (48) van der Heijde, 2023 (49);
†ASAS40 in the TNF-α inhibitor naïve population was not a ranked endpoint in BE MOBILE 1; ‡all between-group differences are adjusted risk differences (percentages) from the logistic regression model for binary endpoints or mean differences vs placebo from the ANCOVA model for continuous endpoints; ¶placebo n=17, BE MOBILE 1 bimekizumab, n=10, BE MOBILE 2 bimekizumab n=37; §BASMI was not a ranked endpoint for BE MOBILE 1.
Abbreviations: AS, ankylosing spondylitis; ASAS20, Assessment of SpondyloArthritis International Society 20%; ASAS40, Assessment of SpondyloArthritis International Society 50%; ASAS5/6, Assessment of SpondyloArthritis International Society 5 out of 6 criteria; ASAS PR, Assessment of SpondyloArthritis International Society partial remission; ASDAS-MI, Ankylosing Spondylitis Disease Activity Score major improvement; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Disease Metrology Index; CfB, change from baseline; IR, inadequate responders; MI, multiple imputation; nr-axSpA, non-radiographic axial spondyloarthritis; NRI, non-responder imputation; NSP, nocturnal spine pain; PCS, physical component summary; Q4W, every 4 weeks; SE, standard error; SF-36, Short-Form 36-item Health Survey; TNF-α, tumour necrosis factor alpha.

C2. PRIORITY: Please provide the following clarifications on Table 20 (CS, page 67)

a) **Why do the OR and confidence intervals reported in this table not match the equivalent ORs in Table 16? For example, for patients with no prior TNF-α inhibitor exposure in BE MOBILE 1, the OR is reported as 3.12 (1.73, 5.62) whereas in Table 16, an OR for the same comparison with the same observed proportions is reported as 3.08 (1.71, 5.54). Please also explain how these ORs were calculated.**

b) **Please check all ORs reported as some seem implausible. For example, the OR for ASAS40 in patients with previous TNF-α inhibitor exposure has been reported as 10.69 (2.00, 6.16).**

c) **Please revise the row and column descriptions in the table to be more informative. For example, it is not immediately obvious that the column labelled 'N' is the total number of patients in the trial and not by treatment arm.**

d) **Please also provide the total number of patients with response in each treatment arm by prior TNF-α inhibitor exposure for each study.**

e) **Please provide equivalent information for response measured as BASDAI50, mean change BASDAI (from baseline), BASFI scores (long-term change over time) and ASAS20.**

A. The primary efficacy analysis that investigated the treatment effect was adjusted for:

- MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+)
- Geographic region (Asia, Eastern Europe, North America, and Western Europe).

The geographic region and MRI/CRP classification were the stratification of the randomisation. The secondary analyses were adjusted on the same categorical factors as the primary analysis. For continuous endpoints, the Baseline value of the endpoint of interest was also included as a covariate where appropriate.

For each subgroup analysis, a logistic regression was fitted involving all model terms from the primary analysis model and additional terms for subgroup and subgroup by treatment interaction.

For each subgroup category and each treatment group, the mean proportion of responders, the adjusted responder rate with associated 95% CI was calculated as the adjusted OR (for the comparison bimekizumab and placebo) and the 95% CI was also be provided. The column heading of Table 20 has been amended to reflect this (Table 21).

B. The OR for ASAS40 in patients with previous TNF-α inhibitor exposure has been corrected to 10.69 (1.49, 76.67) (Table 21).

C. The table layout has been amended (Table 21).

D. In BE MOBILE 1, 10 patients (7.8%) in the bimekizumab arm, and 17 patients (13.5%) in the placebo arm had prior TNF-α inhibitor exposure (49). In BE MOBILE 2, 37 patients (16.7%) in the bimekizumab arm, and 17 patients (15.3%) in the placebo arm had prior TNF-α inhibitor exposure (49). While UCB acknowledge that BE MOBILE 1 and BE MOBILE 2 have few patients with prior TNF-α inhibitor exposure, the relationship between biologic exposure and response to bimekizumab is consistent across the trial network for axSpA, psoriatic arthritis (PsA), and plaque psoriasis (PSO): bimekizumab has similar treatment response regardless of previous biologic treatment (50-55) (Table 20).

Table 20 Bimekizumab response to treatment by TNF- inhibitor exposure in axSpA and PsA

Population	Trial	Outcome (16 weeks, NRI)†	b/tsDMARD naïve response; % (n/N)	b/tsDMARD experienced response; % (n/N)
nr-axSpA	BE MOBILE 1	ASAS40	46.6% (55/118)	60% (6/10)
AS	BE MOBILE 2	ASAS40	45.7% (84/184)	40.5% (15/37)
Nr-axSpA & AS (pooled)	BE MOBILE 1 & BE MOBILE 2 (pooled)	ASAS40	46% (139/302)	44.7% (21/47)
PsA	BE OPTIMAL (TNF-α naïve) & BE COMPLETE (TNF-α experienced)	ACR50	43.9% (189/431)	43.4% (116/267)
PsA	BE OPTIMAL (TNF-α naïve) & BE COMPLETE (TNF-α experienced)	PASI90	61.3% (133/217)	68.8% (121/176)

Source: BE MOBILE 1 (52), BE MOBILE 2 (53) pooled BE MOBILE 1 and BE MOBILE 2 (54), BE OPTIMAL (50), BE COMPLETE (51).
†All response variable numerical components are percentage change from baseline
Abbreviations: ACR, American College of Rheumatology; ASAS, Assessment in SpondyloArthritis international Society; AS, ankylosing spondylitis; bDMARD, biologic disease-modifying anti-rheumatic drug; DOF, data on file; nr-axSpA, non-radiographic axial spondyloarthritis; NRI, non-responder imputation; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis.

In four phase 3 trials in PSO, bimekizumab had similar treatment response in patients having bimekizumab as their first, second or third biologic at week 16 and at week 48 – 56 (55). Patients also had similar Psoriasis Area and Severity Index (PASI) 90, PASI100 and Dermatology Life Quality Index (DLQI) 0/1 response whether they had treatment after TNF-α inhibitor exposure or IL17A exposure (55).

E. Response rates and the total number of patients with response in each treatment arm are provided in Table 21. Adjusted ORs are only available for the primary endpoint (ASAS40) and ASDAS-MI.

Table 21: Corrected version of Table 20: Subgroup analysis of efficacy outcomes at Week 16 by TNF-α inhibitor exposure (OR 95% CI) in BE MOBILE 1 and BE MOBILE 2 (RS)

Endpoint	Study	TNF-α inhibitor exposure	Treatment	Adjusted OR (95% CI) BKZ vs. PBO	Response n/N(%)/ mean change [SE]† (BKZ/PBO)
ASAS40 (NRI)	BE MOBILE 1	Yes	BKZ	10.69 (1.49, 76.67)	6/10 (60.0)
		Yes	PBO	–	2/17 (11.8)
		No	BKZ	3.12 (1.73, 5.62)	55/118 (46.6)
		No	PBO	–	25/109 (22.9)
ASAS40 (NRI)	BE MOBILE 2	Yes	BKZ	3.48 (0.84, 14.40)	15/37 (40.5)
		Yes	PBO	–	3/17 (17.6)
		No	BKZ	2.79 (1.59, 4.91)	84/184 (45.7)
		No	PBO	–	22/94 (23.4)
ASDAS MI (NRI)	BE MOBILE 1	Yes	BKZ	5.86 (0.47, 72.81)	3/10 (30)
		Yes	PBO	–	1/17 (5.9)
		No	BKZ	5.36 (2.23, 12.70)	32/118 (27.1)
		No	PBO	–	8/109 (7.3)
ASDAS MI (NRI)	BE MOBILE 2	Yes	BKZ	2.35 (0.43, 12.77)	8/37 (21.6)
		Yes	PBO	–	2/17 (11.8)
		No	BKZ	8.57 (2.96 24.75)	49/184 (26.6)
		No	PBO	–	4/94 (4.3)
ASAS20 (NRI)	BE MOBILE 1	Yes	BKZ	NA	8/10 (80)
		Yes	PBO	NA	5/17 (29.4)
		No	BKZ	NA	80/118(67.8)
		No	PBO	NA	43/109 (39.4)
ASAS20 (NRI)	BE MOBILE 2	Yes	BKZ	NA	22/37 (59.5)
		Yes	PBO	NA	6/17 (35.3)
		No	BKZ	NA	124/184 (67.4)
		No	PBO	NA	42/94 (44.7)
BASFI CFB (MI)†	BE MOBILE 1	Yes	BKZ	NA	10 (–3.32) [0.85]
		Yes	PBO	NA	17 (–0.47) [0.47]
		No	BKZ	NA	118 (–2.46) [0.22]
		No	PBO	NA	109 (-1.06) [0.19]
BASFI CFB (MI)†	BE MOBILE 2	Yes	BKZ	NA	37 (–1.92) [0.31]
		Yes	PBO	NA	17 (–0.66) [0.41]
		No	BKZ	NA	184 (–2.21) [0.16]
		No	PBO	NA	94 (–1.17) [0.18]
BASDAI50 (NRI)		Yes	BKZ	NA	4/10 (40)
		Yes	PBO	NA	2/17 (11.8)

Endpoint	Study	TNF-α inhibitor exposure	Treatment	Adjusted OR (95% CI) BKZ vs. PBO	Response n/N(%)/ mean change [SE]† (BKZ/PBO)
	BE MOBILE 1	No	BKZ	NA	56/118 (47.5)
		No	PBO	NA	25/108 (23.1)
BASDAI50 (NRI)	BE MOBILE 2	Yes	BKZ	NA	13/37 (35.1)
		Yes	PBO	NA	6/17 (35.3)
		No	BKZ	NA	90/184 (48.9)
		No	PBO	NA	23/94 (24.5)
BASDAI CFB (MI)†	BE MOBILE 1	Yes	BKZ	NA	10 (–3.36) [0.59]
		Yes	PBO	NA	17 (–1.26) [0.49]
		No	BKZ	NA	118 (–3.05) [0.22]
		No	PBO	NA	109 (–1.55) [0.18[
BASDAI CFB (MI)†	BE MOBILE 2	Yes	BKZ	NA	37 (–2.52) [0.29]
		Yes	PBO	NA	17 (–1.95) [0.62]
		No	BKZ	NA	184 (–2.97) [0.16]
		No	PBO	NA	94 (–1.88) [0.18]

Source: UCB data on file (56); UCB data on file (57); UCB data on file (34); UCB data on file (33);
† Mean change
Abbreviations: ASAS20, Assessment of SpondyloArthritis international Society 20% response;ASAS40, Assessment of SpondyloArthritis international Society 40% response; ASDAS MI, Ankylosing Spondylitis Disease Activity Score major improvement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50% response; BASFI, Bath Ankylosing Spondylitis Functional Index; BKZ, bimekizumab; CFB, change from baseline; CI, confidence interval; MI, multiple imputation; NA, not available; NRI, non-responder imputation; OR, odds ratio; PBO, placebo; RS, randomised set; SE, standard error; TNF-α, tumour necrosis factor alpha.

C3. In tables 16-20, Appendix D, should the captions read “b/tsDMARD” instead of “bDMARD”?

Yes. Amended below in Table 22–Table 26.

Table 22: Corrected version of Table 16: Data availability: pure b/tsDMARD-naïve network (Network 1)

Study	Week	ASAS20	ASAS40	ASAS-5/6	ASAS-PR	BASDAI50	ASDAS-ID	ASDAS-MI	ASDAS<2.1	ASDAS-CII	ASDAS-CRP	BASDAI	BASFI	BASMI	MASES	PtGADA	ASQoL	SF-36 PCS	SF-36 MCS	NSP	Fatigue NRS
ABILITY-1	12	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	×	✓	×	×	×
BE MOBILE 1	16	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C-axSpAnd	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
COAST-X	16	✓	✓	×	×	✓	×	×	✓	×	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓
EMBARK	12	✓	✓	✓	✓	✓	✓	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×
GO-AHEAD	16	✓	✓	×	✓	✓	✓	×	×	×	✓	✓	✓	✓	✓	×	✓	✓	✓	×	×
PREVENT	16	×	✓	×	✓	✓	✓	×	×	×	✓	×	×	×	×	×	✓	✓	×	✓	×
RAPID-axSpA	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SELECT-AXIS 2 (Study 2)	14	×	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score (-CII - Clinically important improvement defined as decrease ≥1.1; CRP, score including laboratory measure of CRP level; -ID, Inactive disease defined as <1.3; <2.1, ASDAS score below 2.1 = low disease activity; -MI, Major improvement); ASAS, Assessment of Spondyloarthritis international Society (ASAS20, 20% improvement, ASAS40, 40% improvement, ASAS5/6 improvement of ≥20% in at least five of the six domains; ASAS PR, partial remission); ASQoL, Ankylosing Spondylitis Quality of Life; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50, 50% improvement); BASFI, Bath Ankylosing Spondylitis Functional Index; b/tsDMARD, biological/targeted syntheic disease-modifying antirheumatic drug; MASES, Maastricht Ankylosing Spondylitis Enthesitis; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; Fatigue NRS, Measured using BASDAI Question 1 Numeric Rating Scale; NSP, nocturnal spine pain; PtGADA, Patient's global assessment of disease activity; SPARCC SIJ, Spondyloarthritis Research Consortium of Canada MRI sacroiliac joint; SF-36, Short-Form 36 (mental component summary [MCS] and physical component summary [PCS]).

Table 23: Corrected version of Table 17: Data availability: predominantly b/tsDMARD-naïve network (Network 2)

study	Week	ASAS20	ASAS40	ASAS-5/6	ASAS-PR	BASDAI50	ASDAS-ID	ASDAS-MI	ASDAS<2.1	ASDAS-CII	ASDAS-CRP	BASDAI	BASFI	BASMI	MASES	PtGADA	ASQoL	SF-36 PCS	SF-36 MCS	NSP	Fatigue NRS
ABILITY-1	12	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	×	✓	×	×	×
BE MOBILE 1	16	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C-axSpAnd	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
COAST-X	16	✓	✓	×	×	✓	×	×	✓	×	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓
EMBARK	12	✓	✓	✓	✓	✓	✓	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×
GO-AHEAD	16	✓	✓	×	✓	✓	✓	×	×	×	✓	✓	✓	✓	✓	×	✓	✓	✓	×	×
Haibel 2008	12	✓	✓	×	✓	×	×	×	×	×	×	✓	✓	✓	✓	✓	×	✓	✓	✓	×
PREVENT	16	×	✓	×	✓	✓	✓	×	×	×	✓	×	×	×	×	×	✓	✓	×	✓	×
RAPID-axSpA	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SELECT-AXIS 2 (Study 2)	14	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	×	✓	×	×	✓	✓

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score (-CII - Clinically important improvement defined as decrease ≥1.1; CRP, score including laboratory measure of CRP level; -ID, Inactive disease defined as <1.3; <2.1, ASDAS score below 2.1 = low disease activity; -MI, Major improvement); ASAS, Assessment of Spondyloarthritis international Society (ASAS20, 20% improvement, ASAS40, 40% improvement, ASAS5/6 improvement of ≥20% in at least five of the six domains; ASAS PR, partial remission); ASQoL, Ankylosing Spondylitis Quality of Life; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50, 50% improvement); BASFI, Bath Ankylosing Spondylitis Functional Index; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; CRP, C-reactive protein; MASES, Maastricht Ankylosing Spondylitis Enthesitis; BASMI, Bath Ankylosing Spondylitis Metrology Index; Fatigue NRS, Measured using BASDAI Question 1 Numeric Rating Scale; NSP, nocturnal spine pain; PtGADA, Patient's global assessment of disease activity; SPARCC SIJ, Spondyloarthritis Research Consortium of Canada MRI sacroiliac joint; SF-36, Short-Form 36 (mental component summary [MCS] and physical component summary [PCS]).

Table 24: Corrected version of Table 18: Data availability: pure b/tsDMARD-naïve network (Network 1)

Study	Week	ASAS20	ASAS40	ASAS5/6	ASASPR	BASDAI50	ASDAS-ID	ASDAS-MI	ASDAS<2.1	ASDAS-CII	ASDAS-CRP	BASDAI	BASFI	BASMI	MASES	PtGADA	ASQoL	SF-36 PCS	SF-36 MCS	NSP	Fatigue NRS
ASTRUM†	16	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
ATLAS	12	✓	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bao 2014	14	✓	✓	✓	×	✓	×	×	×	×	×	×	✓	✓	×	×	×	✓	✓	×	×
BE AGILE†	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BE MOBILE 2†	16	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Calin 2004	12	✓	×	×	×	×	×	×	×	×	×	✓	✓	×	×	✓	×	×	×	×	✓
Canadian AS Trial	12	✓	×	×	×	×	×	×	×	×	×	✓	✓	✓	×	✓	×	×	×	×	×
COAST-V	16	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	×	✓	×	✓	✓
Davis 2003	12	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Deodhar 2021†	16	✓	✓	×	×	×	×	×	×	×	✓	×	✓	✓	×	✓	✓	✓	×	×	×
ETN Study 314	12	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	×	×	×	×	×	×	×	✓
GO-RAISE	14	✓	✓	✓	✓	✓	✓	✓	×	×	×	✓	✓	✓	✓	×	×	✓	✓	×	×
Gorman 2002	16	✓	×	×	×	×	×	×	×	×	×	×	✓	×	×	×	×	✓	✓	✓	×
Hu 2012	12	×	×	×	×	×	×	×	×	×	✓	✓	✓	×	×	×	×	×	×	×	×
Huang 2014	12	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	×
Leeds ETN Study	12	×	✓	×	×	✓	×	×	×	×	×	✓	✓	×	×	×	✓	×	×	×	×
MEASURE 2†	16	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	×	×	×	✓	✓	×	✓	✓
MEASURE 4†	16	✓	✓	✓	×	×	×	×	×	×	×	✓	×	×	×	×	✓	✓	×	×	×
MEASURE 5†	16	✓	✓	✓	✓	×	×	×	×	×	×	✓	×	×	×	×	✓	✓	×	×	×
RAPID-axSpA†	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SELECT-AXIS 1	14	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	×	×	✓	×
SPINE	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	×	×	×

van der Heijde 2017	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	×	×
Xue 2022†	16	×	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×

†data were from the b/tsDMARD naïve subgroup

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score (-CII - Clinically important improvement defined as decrease ≥1.1; CRP, score including laboratory measure of CRP level; -ID, Inactive disease defined as <1.3; <2.1, ASDAS score below 2.1 = low disease activity; -MI, Major improvement); ASAS, Assessment of SpondyloArthritis international Society (ASAS20, 20% improvement, ASAS40, 40% improvement, ASAS5/6 improvement of ≥20% in at least five of the six domains; ASAS PR, partial remission); ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50, 50% improvement); BASFI, Bath Ankylosing Spondylitis Functional Index; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; MASES, Maastricht Ankylosing Spondylitis Enthesitis; BASMI, Bath Ankylosing Spondylitis Metrology Index; NSP, nocturnal spine pain; Fatigue NRS, Measured using BASDAI Question 1 Numeric Rating Scale; PtGADA, Patient's global assessment of disease activity; SF-36, Short-Form 36 (mental component summary [MCS] and physical component summary [PCS]).

Table 25: Corrected version of Table 19: Data availability: predominantly b/tsDMARD-naïve network (Network 2)

Study	Week	ASAS20	ASAS40	ASAS5/6	ASAS-PR	BASDAI50	ASDAS-ID	ASDAS-MI	ASDAS<2.1	ASDAS-CII	ASDAS-CRP	BASDAI	BASFI	BASMI	MASES	PtGADA	ASQoL	SF-36 PCS	SF-36 MCS	NSP	Fatigue NRS
ASSERT	12	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
ASTRUM	16	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	×	×	×	×	×	×	×	×	×
ATLAS	12	✓	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bao 2014	14	✓	✓	✓	×	✓	×	×	×	×	×	×	✓	✓	×	×	×	✓	✓	×	×
BE AGILE	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BE MOBILE 2	16	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Calin 2004	12	✓	×	×	×	×	×	×	×	×	×	✓	✓	×	×	✓	×	×	×	×	✓
Canadian AS Trial	12	✓	×	×	×	×	×	×	×	×	×	✓	✓	✓	×	✓	×	×	×	×	×
COAST-V	16	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	×	✓	×	✓	✓
Davis 2003	12	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Deodhar 2021	16	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ETN Study 314	12	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	×	×	×	×	×	×	×	✓
GO-ALIVE	16	✓	✓	✓	✓	✓	✓	×	×	✓	✓	×	✓	✓	×	×	✓	✓	✓	✓	×
GO-RAISE	14	✓	✓	✓	✓	✓	✓	✓	×	×	×	✓	✓	✓	✓	×	×	✓	✓	×	×
Gorman 2002	16	✓	×	×	×	×	×	×	×	×	×	×	✓	×	×	×	×	✓	✓	✓	×
Hu 2012	12	×	×	×	×	×	×	×	×	×	✓	✓	✓	×	×	×	×	×	×	×	×
Huang 2014	12	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	×
Leeds ETN Study	12	×	✓	×	×	✓	×	×	×	×	×	✓	✓	×	×	×	✓	×	×	×	×
MEASURE 2	16	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓	×	×	×	✓	✓	✓	✓	✓
MEASURE 4	16	✓	✓	✓	×	×	×	×	×	×	×	✓	×	×	×	×	✓	✓	×	×	×
MEASURE 5	16	✓	✓	✓	✓	×	×	×	×	×	×	✓	×	×	✓	×	✓	✓	×	×	×
RAPID-axSpA	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

SELECT-AXIS 1	14	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	×	×	✓	×
SPINE	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	×	✓	×
van der Heijde 2017	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	×	×
Xue 2022	16	✓	✓	×	×	×	×	×	×	×	✓	✓	✓	✓	✓	×	×	✓	✓	×	×

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score (-CII - Clinically important improvement defined as decrease ≥1.1; CRP, score including laboratory measure of CRP level; -ID, Inactive disease defined as <1.3; <2.1, ASDAS score below 2.1 = low disease activity; -MI, Major improvement); ASAS, Assessment of SpondyloArthritis international Society (ASAS20, 20% improvement, ASAS40, 40% improvement, ASAS5/6 improvement of ≥20% in at least five of the six domains; ASAS PR, partial remission); ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50, 50% improvement); BASFI, Bath Ankylosing Spondylitis Functional Index; biological/targeted synthetic disease-modifying antirheumatic drug; MASES, Maastricht Ankylosing Spondylitis Enthesitis; BASMI, Bath Ankylosing Spondylitis Metrology Index; NSP, nocturnal spine pain; Fatigue NRS, Measured using BASDAI Question 1 Numeric Rating Scale; PtGADA, Patient's global assessment of disease activity; SF-36, Short-Form 36 (mental component summary [MCS] and physical component summary [PCS]).

Table 26: Corrected version of Table 20: Data availability: b/tsDMARD-experienced network (Network 3)

Study	Week	ASAS20	ASAS40	ASAS56	ASASPR	BASDAI50	ASDASID	ASDAS-MI	ASDAS21	ASDASCII	ASDAS	BASDAI	BASFI	BASMI	MASES	PTGADA	ASQOL	SF36PCS	SF36MCS	NSP	Fatigue
ASTRUM†	16	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BE MOBILE 2†	16	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
COAST-W	16	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	×	✓	×	✓	✓
Deodhar 2021†	16	✓	✓	×	×	×	×	×	×	×	✓	×	✓	✓	×	✓	✓	✓	×	×	×
MEASURE 2†	16	✓	✓	✓	✓	×	×	×	×	×	×	✓	×	×	×	×	✓	✓	×	✓	✓
MEASURE 4†	16	✓	✓	✓	×	×	×	×	×	×	×	✓	×	×	×	×	✓	✓	×	×	×
MEASURE 5†	16	✓	✓	✓	✓	×	×	×	×	×	×	✓	×	×	×	×	✓	✓	×	×	×
RAPID-axSpA†	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SELECT-AXIS 2 (Study 1)	14	✓	✓	×	✓	✓	✓	×	✓	×	✓	✓	✓	✓	✓	✓	✓	×	×	✓	✓

† data were from the b/tsDMARD experienced subgroup

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score (-CII - Clinically important improvement defined as decrease ≥1.1; CRP, score including laboratory measure of CRP level; -ID, Inactive disease defined as <1.3; <2.1, ASDAS score below 2.1 = low disease activity; -MI, Major improvement); ASAS, Assessment of SpondyloArthritis international Society (ASAS20, 20% improvement, ASAS40, 40% improvement, ASAS5/6 improvement of ≥20% in at least five of the six domains; ASAS PR, partial remission); ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50, 50% improvement); BASFI, Bath Ankylosing Spondylitis Functional Index; biological/targeted synthetic disease-modifying antirheumatic drug; MASES, Maastricht Ankylosing Spondylitis Enthesitis; BASMI, Bath Ankylosing Spondylitis Metrology Index; NSP, nocturnal spine pain; Fatigue NRS, Measured using BASDAI Question 1 Numeric Rating Scale; PtGADA, Patient's global assessment of disease activity SF-36, Short-Form 36 (mental component summary [MCS] and physical component summary [PCS]).

C4. The evidence sources used to inform the response rates in the cost-comparison model do not appear to match the populations in Table 31 (CS), as it suggests that BE MOBILE 1 and BE MOBILE 2 were used to inform the response rates for AS and nr-axSpA response rates populations. Could you please confirm this was just a labelling issue and correct accordingly.

We can confirm that this was a labelling issue; a corrected version of Table 31 is provided in Table 27.

Table 27: Corrected version of Table 31 (BASDAI50 and ASAS40 response rates)

	BASDAI50 response	ASAS40 response	Source
Nr-axSpA	46.9%	47.7%	BE MOBILE 1 (21)
AS	46.6%	44.8%	BE MOBILE 2 (22)

Abbreviations: AS, ankylosing spondylitis; nr-axSpA, BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50%; nr-axSpA, non-radiographic axial spondyloarthritis.

Missing files

C5. In Appendix D.1.8.2 Excluded Studies, it states that a list is provided as a separate excel file. We have been unable to locate this file, please can it be provided?

Provided in file 'UCB. Data on file. Excluded studies list'.

C6. The report 'Bimekizumab for the treatment of ankylosing spondylitis: 2023 SLR and NMA update. Date of preparation: 28th April 2023 Version: 3.0 (Document 1 of 5)' included in reference pack 2 of the company submission, references the following 2 systematic reviews:

9. Evidera/UCB. An Update to a Systematic Review of Bimekizumab and Biological and Targeted Synthetic DMARDs in the Treatment of Ankylosing Spondylitis (EVA-24600, October 29 2021, Version 2.0).

10. Evidera/UCB. An Update to a Systematic Review of Cimzia® and Biological DMARDs in the Treatment of Non-radiographic Axial Spondyloarthritis (EVA-24600, September 10 2021, Version 2.0).

Please could these 2 reports by Evidera/UCB be provided?

These have now been provided.

C7. PRIORITY: Some key files in the company's original submission are corrupted (they have 0KB and do not open). Please provide the files listed below again, ensuring all references can be opened:

a) **Excel spreadsheet "RxY. Data on file. CONFIDENTIAL. AxSpA market share analysis. 2022"(8)**

b) **Baraliakos 2022 ACR - AS10_11 w52 efficacy & safety abstract.pdf**

c) **Baraliakos 2022 ACR - AS10_11 w52 efficacy & safety POS-1.pdf**

d) **Baraliakos 2022 Effect of secukinumab versus adalimumab.pdf**

e) **DHS Women's Health Strategy for England 17-Healthy ageing 2021.pdf**

f) **DHS Our Vision for the Women's Health Strategy for England 2021.pdf**

g) **Howard Wilsher 2022 Economic cost of delayed diagnosis axSpA UK.pdf**

h) **Navarro-Compán 2022 BE AGILE 3yr BKZ Maintenance of response [poster].pdf**

i) **Su 2020 Comparison_of_the_Efficacy_and_Safety_of_Adalimuma.pdf**

These have now been provided.

C8. PRIORITY: The following appendices are missing from the company's NMA reports for AS and nr-axSpA. Please provide the files listed below:

a) **Appendix 5: Safety and tolerability data NMA (2023) and Appendix 6: Additional exploratory analyses (2023) in the file: "UCB. Data on File. CONFIDENTIAL. AS NMA report.2023"**

b) **Appendix 4: Safety and tolerability data NMA (2023) and Appendix 5: Additional exploratory analyses (2023) in the file "UCB. Data on file. CONFIDENTIAL. Nr-axSpA NMA report. 2023"**

UCB have provided these in uploaded NMA reports for nr-axSpA and AS.

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Appendix 1: SLR search strategy

1.1 Original SLR: May 2012

1.1.1 MEDLINE/CENTRAL search strategy

Table 28: Original May 2012 SLR – MEDLINE/CENTRAL axSpA search strategy

Search	MEDLINE/CENTRAL† PsA Search Algorithm
#1	"Antirheumatic Agents"[Mesh] OR "biological disease-modifying anti-rheumatic drugs"[tiab] OR "disease-modifying anti-rheumatic drugs"[tiab] OR “disease modifying antirheumatic drug*"[tiab] OR DMARD[tiab] OR "TNF inhibitor"[tiab] OR "anti-TNF"[tiab] OR "tumor necrosis factor*"[tiab] OR "tumour necrosis factor*"[tiab] OR TNF-alpha[tiab] OR TNF-a[tiab] OR TNF-α[tiab] OR “TNF-antagonist"[tiab]
#2	adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade

#3	ankylos*[tiab] OR spondyl*[tiab] OR spondyloarthropath*[tiab] OR spondylarthropath*[tiab] OR spondylarthrit*[tiab] OR "Bechterew* disease"[tiab] OR "Marie-Struempell* disease"[tiab] OR "Marie Struempell* disease"[tiab] OR "rheum* spondylitis"[tiab] OR "axial SpA"[tiab]
#4	#1 (#1 OR #2) AND #3
#5	#4 AND random*[tiab]
#6	#5 limit: review
#7	#5 NOT #6
#8	#7 limit: English

†The medical subject heading (MESH) terms used in the PubMed search (above) was used as free text to search the CENTRAL database.

1.1.2 Embase search strategy

Table 29: Original May 2012 SLR – EMBASE axSpA search strategy

Search	EMBASE axSpA Search Algorithm
#1	'antirheumatic agent'/exp OR 'antirheumatic agent':ab,ti OR 'tumor necrosis factor inhibitor'/exp OR 'biological disease-modifying anti-rheumatic drugs':ab,ti OR 'disease-modifying anti-rheumatic drugs':ab,ti OR DMARD:ab,ti OR 'TNF inhibitor':ab,ti OR 'anti-TNF':ab,ti OR 'tumor necrosis factor':ab,ti OR 'tumour necrosis factor':ab,ti OR TNF-alpha:ab,ti OR TNF-a:ab,ti OR TNF-α:ab,ti OR TNF-antagonist;ab,ti
#2	'adalimumab'/exp OR adalimumab:ab,ti OR Humira:ab,ti OR 'certolizumab pegol'/exp OR certolizumab:ab,ti OR cimzia:ab,ti OR CDP870:ab,ti OR 'etanercept'/exp OR etanercept:ab,ti OR Enbrel:ab,ti OR 185243-69-0:ab,ti OR 'golimumab'/exp OR golimumab:ab,ti OR Simponi:ab,ti OR 'infliximab'/exp OR infliximab:ab,ti OR Remicade:ab,ti
#3	ankylos*:ab,ti OR spondyl*:ab,ti OR spondyloarthropath*:ab,ti OR spondylarthropath*:ab,ti OR spondylarthrit*:ab,ti OR 'Bechterew* disease':ab,ti OR 'Marie-Struempell* disease':ab,ti OR 'Marie Struempell* disease':ab,ti OR 'rheum* spondylitis':ab,ti OR 'axial SpA':ab,ti OR 'axial SpA':ab,ti
#4	#1 (#1 OR #2) AND #3
#5	#4 AND Random*:ab,ti
#6	#5 limit: review
#7	#5 NOT #6
#8	#7 limit: English

1.2 October 2013 SLR update

1.2.1 MEDLINE search strategy

Table 30: October 2013 SLR update – MEDLINE search strategy

#	Search Terms
#1	"Antirheumatic Agents"[Mesh] OR "biological disease-modifying anti-rheumatic drugs"[tiab] OR "disease-modifying anti-rheumatic drugs"[tiab] OR “disease modifying antirheumatic drug*"[tiab] OR DMARD[tiab] OR "TNF inhibitor"[tiab] OR "anti-TNF"[tiab] OR "tumor necrosis factor*"[tiab] OR "tumour necrosis factor*"[tiab] OR TNF-alpha[tiab] OR TNF-a[tiab] OR TNF-α[tiab] OR "TNF-antagonist"[tiab]
#2	adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade

#	Search Terms
#3	ankylos*[tiab] OR spondyl*[tiab] OR spondyloarthropath*[tiab] OR spondylarthropath*[tiab] OR spondylarthrit*[tiab] OR "Bechterew* disease"[tiab] OR "Marie-Struempell* disease"[tiab] OR "Marie Struempell* disease"[tiab] OR "rheum* spondylitis"[tiab] OR "axial SpA"[tiab]
#4	#1 (#1 OR #2) AND #3
#5	#4 AND random*[tiab]
#6	#5 limit: review
#7	#5 NOT #6
#8	#7 limit: English
#9	#7 limit: English; Publication date from 1991/01/01

1.2.2 Embase search strategy

Table 31: October 2013 SLR update – Embase search strategy

#	Search Terms
#1	'antirheumatic agent'/exp OR 'antirheumatic agent':ab,ti OR 'tumor necrosis factor inhibitor'/exp OR 'biological disease-modifying anti-rheumatic drugs':ab,ti OR 'disease-modifying anti-rheumatic drugs':ab,ti OR DMARD:ab,ti OR 'TNF inhibitor':ab,ti OR 'anti-TNF':ab,ti OR 'tumor necrosis factor':ab,ti OR 'tumour necrosis factor':ab,ti OR TNF-alpha:ab,ti OR TNF-a:ab,ti OR TNF-α:ab,ti OR TNF-antagonist;ab,ti
#2	'adalimumab'/exp OR adalimumab:ab,ti OR Humira:ab,ti OR 'certolizumab pegol'/exp OR certolizumab:ab,ti OR cimzia:ab,ti OR CDP870:ab,ti OR 'etanercept'/exp OR etanercept:ab,ti OR Enbrel:ab,ti OR 185243-69-0:ab,ti OR 'golimumab'/exp OR golimumab:ab,ti OR Simponi:ab,ti OR 'infliximab'/exp OR infliximab:ab,ti OR Remicade:ab,ti
#3	ankylos*:ab,ti OR spondyl*:ab,ti OR spondyloarthropath*:ab,ti OR spondylarthropath*:ab,ti OR spondylarthrit*:ab,ti OR 'Bechterew* disease':ab,ti OR 'Marie-Struempell* disease':ab,ti OR 'Marie Struempell* disease':ab,ti OR 'rheum* spondylitis':ab,ti OR 'axial SpA':ab,ti OR 'axial SpA':ab,ti
#4	#1 (#1 OR #2) AND #3
#5	#4 AND Random*:ab,ti
#6	#5 limit: review
#7	#5 NOT #6
#8	#7 limit: English AND [1991-2014]/py

1.2.3 CENTRAL search strategy

Table 32: October 2013 SLR update – CENTRAL search strategy

#	Search terms
#1	MeSH descriptor: [Antirheumatic Agents] explode all trees
#2	"biological disease-modifying anti-rheumatic drugs":ti,ab OR "disease-modifying anti-rheumatic drugs":ti,ab OR “disease modifying antirheumatic drug*":ti,ab OR DMARD:ti,ab OR "TNF inhibitor":ti,ab OR "anti-TNF":ti,ab OR "tumor necrosis factor*":ti,ab OR "tumour necrosis factor*":ti,ab OR TNF-alpha:ti,ab OR TNF-a:ti,ab OR TNF-α:ti,ab OR "TNF-antagonist":ti,ab
#3	#1 OR #2

#	Search terms
#4	adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade
#5	ankylos*:ti,ab OR spondyl*:ti,ab OR spondyloarthropath*:ti,ab OR spondylarthropath*:ti,ab OR spondylarthrit*:ti,ab OR "Bechterew* disease":ti,ab OR "Marie-Struempell* disease":ti,ab OR "Marie Struempell* disease":ti,ab OR "rheum* spondylitis":ti,ab OR "axial SpA":ti,ab
#6	#1 (#3 OR #4) AND #5
#7	#6 AND random*:ti,ab
#8	#7 limit: review
#9	#7 NOT #8
#10	#9 limit: in Trials; Publication date from 1991/01/01

1.3 July 2017 SLR update

1.3.1 PubMed search strategy

Table 33: July 2014 SLR update – PubMed search strategy

#	Search Terms	Hits
#1	Search ("Antirheumatic Agents"[Mesh] OR "biological disease-modifying anti-rheumatic drugs"[tiab] OR "disease-modifying anti-rheumatic drugs"[tiab] OR “disease modifying antirheumatic drug*"[tiab] OR DMARD[tiab] OR "TNF inhibitor"[tiab] OR "anti-TNF"[tiab] OR "tumor necrosis factor*"[tiab] OR "tumour necrosis factor*"[tiab] OR TNF-alpha[tiab] OR TNF-a[tiab] OR TNF-α[tiab] OR "TNF-antagonist"[tiab])	216618
#2	Search (adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade)	14172
#3	Search (ankylos*[tiab] OR spondyl*[tiab] OR spondyloarthropath*[tiab] OR spondylarthropath*[tiab] OR spondylarthrit*[tiab] OR "Bechterew* disease"[tiab] OR "Marie-Struempell* disease"[tiab] OR "Marie Struempell* disease"[tiab] OR "rheum* spondylitis"[tiab] OR "axial SpA"[tiab])	31376
#4	Search ((#1 OR #2) AND #3)	2714
#5	Search (#4 AND random*[tiab])	331
#6	Search (#4 AND random*[tiab]) Filters: Review	81
#7	Search (#5 NOT #6)	250
#8	Search (#5 NOT #6) Filters: English	232
#9	Search (#5 NOT #6) Filters: Publication date from 1991/01/01; English	229

1.3.2 Embase search strategy

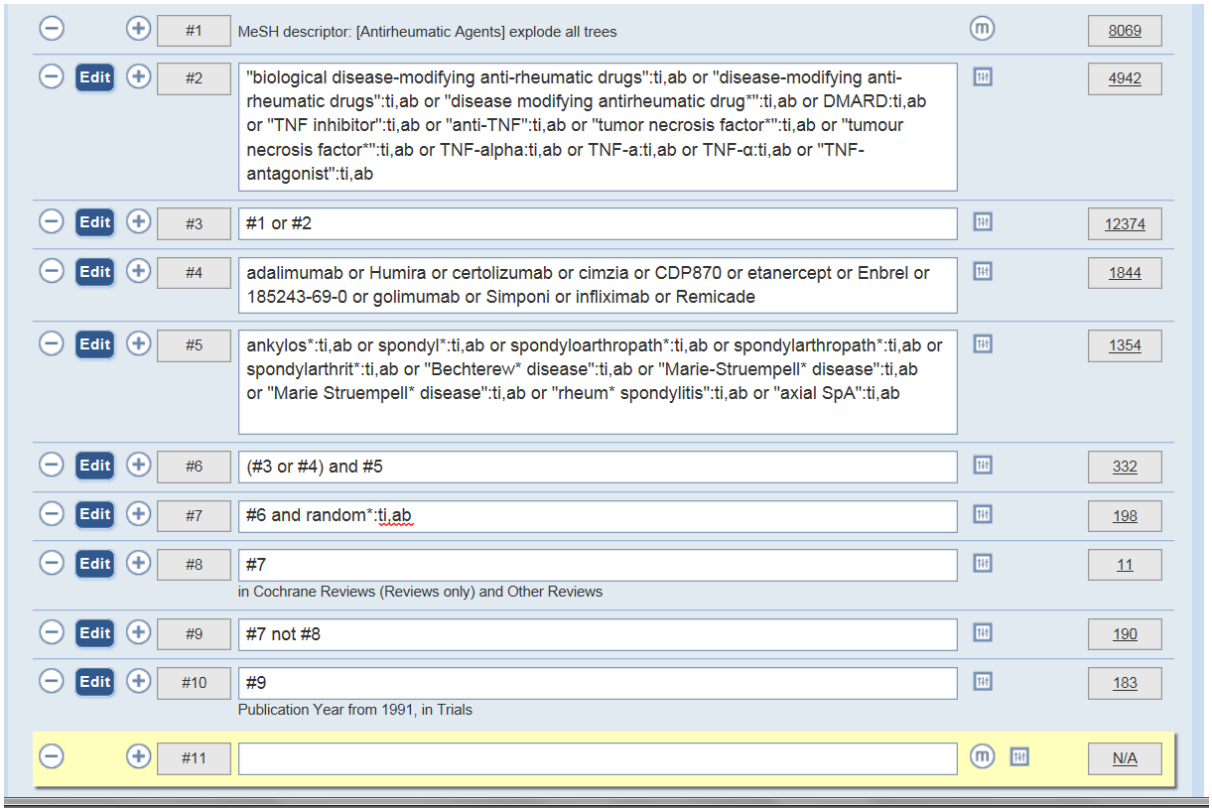
Table 34: July 2014 SLR update – Embase search strategy

#	Search Terms	Hits
#8	#7 AND [english]/lim AND [1991-2014]/py	477
#7	#5 NOT #6	517
#6	#5 AND 'review'/it	83

#	Search Terms	Hits
#5	#4 AND random*:ab,ti	600
#4	#1 OR #2 AND #3	5269
#3	ankylos*:ab,ti OR spondyl*:ab,ti OR spondyloarthropath*:ab,ti OR spondylarthropath*:ab,ti OR spondylarthrit*:ab,ti OR 'bechterew next/1 disease':ab,ti OR 'marie next/1 struempell':ab,ti OR 'rheum next/1 spondylitis':ab,ti OR 'axial spa':ab,ti	40448
#2	'adalimumab'/exp OR adalimumab:ab,ti OR humira:ab,ti OR 'certolizumab pegol'/exp OR certolizumab:ab,ti OR cimzia:ab,ti OR cdp870:ab,ti OR 'etanercept'/exp OR etanercept:ab,ti OR enbrel:ab,ti OR '185243 69 0':ab,ti OR 'golimumab'/exp OR golimumab:ab,ti OR simponi:ab,ti OR 'infliximab'/exp OR infliximab:ab,ti OR remicade:ab,ti	41330
#1	'antirheumatic agent'/exp OR 'antirheumatic agent':ab,ti OR 'tumor necrosis factor inhibitor'/exp OR 'biological disease-modifying anti-rheumatic drugs':ab,ti OR 'disease-modifying anti-rheumatic drugs':ab,ti OR dmard:ab,ti OR 'tnf inhibitor':ab,ti OR 'anti-tnf':ab,ti OR 'tumor necrosis factor':ab,ti OR 'tumour necrosis factor':ab,ti OR 'tnf alpha':ab,ti OR 'tnf a':ab,ti OR 'tnf α':ab,ti OR 'tnf antagonist;ab,ti'	573728

1.3.3 MEDLINE search strategy

Table 35: July 2014 SLR update – CENTRAL search strategy



1.4 January 2017 SLR update

1.4.1 MEDLINE search strategy

Table 36: January 2017 SLR update – MEDLINE search strategy

#	Search Terms
#1	"Antirheumatic Agents"[Mesh] OR "biological disease-modifying anti-rheumatic drugs"[tiab] OR "disease-modifying anti-rheumatic drugs"[tiab] OR “disease modifying antirheumatic drug*"[tiab] OR DMARD[tiab] OR "TNF inhibitor"[tiab] OR "anti-TNF"[tiab] OR "tumor necrosis factor*"[tiab] OR "tumour necrosis factor*"[tiab] OR TNF-alpha[tiab] OR TNF-a[tiab] OR TNF-α[tiab] OR "TNF-antagonist"[tiab]
#2	adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade OR secukinumab OR cosentyx OR AIN457 OR (("Biosimilar Pharmaceuticals"[Mesh] OR biosimila*) AND ("TNF inhibitor"[tiab] OR "anti-TNF"[tiab] OR “tumor necrosis factor*”[tiab] OR TNF-alpha[tiab] OR TNF-a[tiab] OR TNF-α[tiab] OR “TNF-antagonist”[tiab]))
#3	ankylos*[tiab] OR spondyl*[tiab] OR spondyloarthropath*[tiab] OR spondylarthropath*[tiab] OR spondylarthrit*[tiab] OR "Bechterew* disease"[tiab] OR "Marie-Struempell* disease"[tiab] OR "Marie Struempell* disease"[tiab] OR "rheum* spondylitis"[tiab] OR "axial SpA"[tiab]
#4	(#1 OR #2) AND #3
#5	#4 AND random*[tiab]
#6	#5 limit: review
#7	#5 NOT #6
#8	#7 limit: English
#9	#7 limit: English; Publication date from 1991/01/01

1.4.2 Embase search strategy

Table 37: January 2017 SLR update – Embase search strategy

#	Search Terms
#1	'antirheumatic agent'/exp OR 'antirheumatic agent':ab,ti OR 'tumor necrosis factor inhibitor'/exp OR 'biological disease-modifying anti-rheumatic drugs':ab,ti OR 'disease-modifying anti-rheumatic drugs':ab,ti OR DMARD:ab,ti OR 'TNF inhibitor':ab,ti OR 'anti-TNF':ab,ti OR 'tumor necrosis factor':ab,ti OR 'tumour necrosis factor':ab,ti OR TNF-alpha:ab,ti OR TNF-a:ab,ti OR TNF-α:ab,ti OR TNF-antagonist;ab,ti
#2	'adalimumab'/exp OR adalimumab:ab,ti OR Humira:ab,ti OR 'certolizumab pegol'/exp OR certolizumab:ab,ti OR cimzia:ab,ti OR CDP870:ab,ti OR 'etanercept'/exp OR etanercept:ab,ti OR Enbrel:ab,ti OR 185243-69-0:ab,ti OR 'golimumab'/exp OR golimumab:ab,ti OR Simponi:ab,ti OR 'infliximab'/exp OR infliximab:ab,ti OR Remicade:ab,ti OR 'secukinumab'/exp OR secukinumab:ab,ti OR Cosentyx:ab,ti OR AIN457:at,ti OR ('biosimilar agent'/exp AND ('TNF inhibitor':ti,ab OR 'anti-TNF':ti,ab OR ‘tumor necrosis factor’:ti,ab OR ‘tumour necrosis factor’:ti,ab OR TNF-alpha:ti,ab OR TNF-a:ti,ab OR TNF-α:ti,ab OR TNF-antagonist:ti,ab))
#3	ankylos*:ab,ti OR spondyl*:ab,ti OR spondyloarthropath*:ab,ti OR spondylarthropath*:ab,ti OR spondylarthrit*:ab,ti OR 'Bechterew* disease':ab,ti OR 'Marie-Struempell* disease':ab,ti OR 'Marie Struempell* disease':ab,ti OR 'rheum* spondylitis':ab,ti OR 'axial SpA':ab,ti OR 'axial SpA':ab,ti
#4	(#1 OR #2) AND #3
#5	#4 AND Random*:ab,ti
#6	#5 limit: review
#7	#5 NOT #6

#	Search Terms
#8	#7 limit: English AND [1991-2016]/py

1.4.3 CENTRAL search strategy

Table 38: January 2017 SLR update – CENTRAL search strategy

#	Search terms
#1	MeSH descriptor: [Antirheumatic Agents] explode all trees
#2	"biological disease-modifying anti-rheumatic drugs":ti,ab OR "disease-modifying anti-rheumatic drugs":ti,ab OR “disease modifying antirheumatic drug*":ti,ab OR DMARD:ti,ab OR "TNF inhibitor":ti,ab OR "anti-TNF":ti,ab OR "tumor necrosis factor*":ti,ab OR "tumour necrosis factor*":ti,ab OR TNF-alpha:ti,ab OR TNF-a:ti,ab OR TNF-α:ti,ab OR "TNF-antagonist":ti,ab
#3	#1 OR #2
#4	adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade OR secukinumab OR cosentyx OR AIN457 OR (("Biosimilar Pharmaceuticals"[Mesh] OR biosimila*) AND ('TNF inhibitor':ti,ab OR 'anti-TNF':ti,ab OR ‘tumor necrosis factor’:ti,ab OR ‘tumour necrosis factor’:ti,ab OR TNF-alpha:ti,ab OR TNF-a:ti,ab OR TNF-α:ti,ab OR TNF-antagonist:ti,ab))
#5	ankylos*:ti,ab OR spondyl*:ti,ab OR spondyloarthropath*:ti,ab OR spondylarthropath*:ti,ab OR spondylarthrit*:ti,ab OR "Bechterew* disease":ti,ab OR "Marie-Struempell* disease":ti,ab OR "Marie Struempell* disease":ti,ab OR "rheum* spondylitis":ti,ab OR "axial SpA":ti,ab
#6	(#3 OR #4) AND #5
#7	#6 AND random*:ti,ab
#8	#7 limit: review
#9	#7 NOT #8
#10	#9 limit: in Trials; Publication date from 1991/01/01

1.5 June 2018 SLR update

1.5.1 MEDLINE search strategy

Table 39: June 2018 SLR update – MEDLINE search string

#	Search terms
#1	"Antirheumatic Agents"[Mesh] OR "biological disease-modifying anti-rheumatic drugs"[tiab] OR "disease-modifying anti-rheumatic drugs"[tiab] OR “disease modifying antirheumatic drug*"[tiab] OR DMARD[tiab] OR "TNF inhibitor"[tiab] OR "anti-TNF"[tiab] OR "tumor necrosis factor*"[tiab] OR "tumour necrosis factor*"[tiab] OR TNF-alpha[tiab] OR TNF-a[tiab] OR TNF-α[tiab] OR "TNF-antagonist"[tiab]
#2	adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade OR secukinumab OR cosentyx OR AIN457 OR (("Biosimilar Pharmaceuticals"[Mesh] OR biosimila*) AND ("TNF inhibitor"[tiab] OR "anti-TNF"[tiab] OR “tumor necrosis factor*”[tiab] OR TNF-alpha[tiab] OR TNF-a[tiab] OR TNF-α[tiab] OR “TNF-antagonist”[tiab]))
#3	ankylos*[tiab] OR spondyl*[tiab] OR spondyloarthropath*[tiab] OR spondylarthropath*[tiab] OR spondylarthrit*[tiab] OR "Bechterew* disease"[tiab] OR "Marie-Struempell* disease"[tiab] OR "Marie Struempell* disease"[tiab] OR "rheum* spondylitis"[tiab] OR "axial SpA"[tiab]
#4	(#1 OR #2) AND #3

#	Search terms
#5	#4 AND random*[tiab]
#6	#5 limit: review
#7	#5 NOT #6
#8	#7 limit: English
#9	#7 limit: English; Publication date from 2017/01/12

1.5.2 Embase search strategy

Table 40: May 2022 SLR update – Embase search string

#	Search terms
#1	'antirheumatic agent'/exp OR 'antirheumatic agent':ab,ti OR 'tumor necrosis factor inhibitor'/exp OR 'biological disease-modifying anti-rheumatic drugs':ab,ti OR 'disease-modifying anti-rheumatic drugs':ab,ti OR DMARD:ab,ti OR 'TNF inhibitor':ab,ti OR 'anti-TNF':ab,ti OR 'tumor necrosis factor':ab,ti OR 'tumour necrosis factor':ab,ti OR TNF-alpha:ab,ti OR TNF-a:ab,ti OR TNF-α:ab,ti OR TNF-antagonist;ab,ti
#2	'adalimumab'/exp OR adalimumab:ab,ti OR Humira:ab,ti OR 'certolizumab pegol'/exp OR certolizumab:ab,ti OR cimzia:ab,ti OR CDP870:ab,ti OR 'etanercept'/exp OR etanercept:ab,ti OR Enbrel:ab,ti OR 185243-69-0:ab,ti OR 'golimumab'/exp OR golimumab:ab,ti OR Simponi:ab,ti OR 'infliximab'/exp OR infliximab:ab,ti OR Remicade:ab,ti OR 'secukinumab'/exp OR secukinumab:ab,ti OR Cosentyx:ab,ti OR AIN457:at,ti OR ('biosimilar agent'/exp AND ('TNF inhibitor':ti,ab OR 'anti-TNF':ti,ab OR ‘tumor necrosis factor’:ti,ab OR ‘tumour necrosis factor’:ti,ab OR TNF-alpha:ti,ab OR TNF-a:ti,ab OR TNF-α:ti,ab OR TNF-antagonist:ti,ab))
#3	ankylos*:ab,ti OR spondyl*:ab,ti OR spondyloarthropath*:ab,ti OR spondylarthropath*:ab,ti OR spondylarthrit*:ab,ti OR 'Bechterew* disease':ab,ti OR 'Marie-Struempell* disease':ab,ti OR 'Marie Struempell* disease':ab,ti OR 'rheum* spondylitis':ab,ti OR 'axial SpA':ab,ti OR 'axial SpA':ab,ti
#4	(#1 OR #2) AND #3
#5	#4 AND Random*:ab,ti
#6	#5 limit: review
#7	#5 NOT #6
#8	#7 limit: English AND [1991-2016]/py

1.6 April 2019 SLR update

1.6.1 CENTRAL search strategy

Table 41: April 2019 SLR update – MEDLINE search string

#	Search terms
#1	"Antirheumatic Agents"[Mesh] OR "biological disease-modifying anti-rheumatic drugs"[tiab] OR "disease-modifying anti-rheumatic drugs"[tiab] OR “disease modifying antirheumatic drug*"[tiab] OR DMARD[tiab] OR "TNF inhibitor"[tiab] OR "anti-TNF"[tiab] OR "tumor necrosis factor*"[tiab] OR "tumour necrosis factor*"[tiab] OR TNF-alpha[tiab] OR TNF-a[tiab] OR TNF-α[tiab] OR "TNF-antagonist"[tiab]
#2	adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade OR secukinumab OR cosentyx OR AIN457 OR ixekizumab OR taltz OR LY2439821 OR LY-2439821 OR (("Biosimilar Pharmaceuticals"[Mesh] OR biosimila*) AND ("TNF inhibitor"[tiab] OR "anti-TNF"[tiab] OR “tumor necrosis factor*”[tiab] OR TNF-alpha[tiab] OR TNF-a[tiab] OR TNF-α[tiab] OR “TNF-antagonist”[tiab]))

#	Search terms
#3	ankylos*[tiab] OR spondyl*[tiab] OR spondyloarthropath*[tiab] OR spondylarthropath*[tiab] OR spondylarthrit*[tiab] OR "Bechterew* disease"[tiab] OR "Marie-Struempell* disease"[tiab] OR "Marie Struempell* disease"[tiab] OR "rheum* spondylitis"[tiab] OR "axial SpA"[tiab]
#4	(#1 OR #2) AND #3
#5	#4 AND random*[tiab]
#6	#5 limit: review
#7	#5 NOT #6
#8	#7 limit: English
#9	#7 limit: English; Publication date from 2018/05/01

1.6.2 Embase search strategy

Table 42: April 2019 SLR update – Embase search string

#	Search terms
#1	'antirheumatic agent'/exp OR 'antirheumatic agent':ab,ti OR 'tumor necrosis factor inhibitor'/exp OR 'biological disease-modifying anti-rheumatic drugs':ab,ti OR 'disease-modifying anti-rheumatic drugs':ab,ti OR DMARD:ab,ti OR 'TNF inhibitor':ab,ti OR 'anti-TNF':ab,ti OR 'tumor necrosis factor':ab,ti OR 'tumour necrosis factor':ab,ti OR TNF-alpha:ab,ti OR TNF-a:ab,ti OR TNF-α:ab,ti OR TNF-antagonist;ab,ti
#2	'adalimumab'/exp OR adalimumab:ab,ti OR Humira:ab,ti OR 'certolizumab pegol'/exp OR certolizumab:ab,ti OR cimzia:ab,ti OR CDP870:ab,ti OR 'etanercept'/exp OR etanercept:ab,ti OR Enbrel:ab,ti OR 185243-69-0:ab,ti OR 'golimumab'/exp OR golimumab:ab,ti OR Simponi:ab,ti OR 'infliximab'/exp OR infliximab:ab,ti OR Remicade:ab,ti OR 'secukinumab'/exp OR secukinumab:ab,ti OR Cosentyx:ab,ti OR AIN457:ab,ti OR ‘ixekizumab’/exp OR ixekizumab:ab,ti OR taltz:ab,ti OR LY2439821:ab,ti OR LY-2439821:ab,ti OR ('biosimilar agent'/exp AND ('TNF inhibitor':ti,ab OR 'anti-TNF':ti,ab OR ‘tumor necrosis factor’:ti,ab OR ‘tumour necrosis factor’:ti,ab OR TNF-alpha:ti,ab OR TNF-a:ti,ab OR TNF-α:ti,ab OR TNF-antagonist:ti,ab))
#3	ankylos*:ab,ti OR spondyl*:ab,ti OR spondyloarthropath*:ab,ti OR spondylarthropath*:ab,ti OR spondylarthrit*:ab,ti OR 'Bechterew* disease':ab,ti OR 'Marie-Struempell* disease':ab,ti OR 'Marie Struempell* disease':ab,ti OR 'rheum* spondylitis':ab,ti OR 'axial SpA':ab,ti OR 'axial SpA':ab,ti
#4	(#1 OR #2) AND #3
#5	#4 AND Random*:ab,ti
#6	#5 AND 'review'/it
#7	#5 NOT #6
#8	#7 AND [english]/lim AND [1991-2019]/py AND [1-5-2018]/sd

1.6.3 CENTRAL search strategy

Table 43: April 2019 SLR update – CENTRAL search strategy

#	Search terms
#1	MeSH descriptor: [Antirheumatic Agents] explode all trees
#2	"biological disease-modifying anti-rheumatic drugs":ti,ab OR "disease-modifying anti-rheumatic drugs":ti,ab OR “disease modifying antirheumatic drug*":ti,ab OR DMARD:ti,ab OR "TNF inhibitor":ti,ab OR "anti-TNF":ti,ab OR "tumor necrosis factor*":ti,ab OR "tumour

#	Search terms
	necrosis factor*":ti,ab OR TNF-alpha:ti,ab OR TNF-a:ti,ab OR TNF-α:ti,ab OR "TNF-antagonist":ti,ab
#3	#1 OR #2
#4	adalimumab or Humira or certolizumab or cimzia or CDP870 or etanercept or Enbrel or 185243-69-0 or golimumab or Simponi or infliximab or Remicade or ixekizumab or Taltz or secukinumab or cosentyx or AIN457
#5	MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees
#6	#5 or biosimila*
#7	'TNF inhibitor':ti,ab or 'anti-TNF':ti,ab or 'tumor necrosis factor':ti,ab or 'tumour necrosis factor':ti,ab or TNF-alpha:ti,ab or TNF-a:ti,ab or TNF-α:ti,ab or TNF-antagonist:ti,ab
#8	#6 and #7
#9	#4 or #8
#10	ankylos*:ti,ab or spondyl*:ti,ab or spondyloarthropath*:ti,ab or spondylarthropath*:ti,ab or spondylarthrit*:ti,ab or "Bechterew* disease":ti,ab or "Marie-Struempell* disease":ti,ab or "Marie Struempell* disease":ti,ab or "rheum* spondylitis":ti,ab or "axial SpA":ti,ab
#11	(#3 or #9) and #10
#12	#11 and random*:ti,ab
#13	#12: limit review
#14	#12 not #13
#15	#14 Publication Year from 2018 to 2019 (Word variations have been searched)

1.7 October 2020 SLR update

1.7.1 MEDLINE search strategy

Table 44: October 2020 SLR update – MEDLINE search string

#	Search terms
#1	Exp Antirheumatic Agents/ OR exp Interleukin-17/ OR (biological disease-modifying anti-rheumatic drugs OR disease-modifying anti-rheumatic drugs OR disease modifying antirheumatic drug$ OR DMARD$ OR TNF inhibitor$ OR anti-TNF OR tumor necrosis factor$ OR tumour necrosis factor$ OR TNF-alpha OR TNF-a OR TNF-α OR TNF-antagonist).ti,ab.
#2	exp adalimumab/ or exp certolizumab pegol/ or exp etanercept/ or exp golimumab/ or exp infliximab/ or exp secukinumab/ or exp ixekizumab or (adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade OR secukinumab OR cosentyx OR AIN457 OR ixekizumab OR taltz OR LY2439821 OR LY-2439821).ti,ab. OR ((exp Biosimilar Pharmaceuticals/ OR biosimila$.ti,ab.) AND (TNF inhibitor OR anti-TNF OR tumor necrosis factor$ OR TNF-alpha OR TNF-a OR TNF-α OR TNF-antagonist).ti,ab.)
#3	(ankylos$ OR spondyl$ OR spondyloarthropath$ OR spondylarthropath$ OR spondylarthrit$ OR Bechterew$ disease OR Marie-Struempell$ disease OR rheum$ spondylitis OR axial SpA).ti,ab.
#4	(1 OR 2) AND 3
#5	4 AND random$.ti,ab.
#6	review.pt. not (((systematic or meta) and analy$) or ((indirect or mixed) and treatment comparison)).ti,ab.

#	Search terms
#7	5 NOT 6
#8	Limit 7 to English language
#9	Limit 8 to yr=”2019-current”

1.7.2 Embase search strategy

Table 45: October 2020 SLR update – Embase search string

#	Search terms
#1	exp antirheumatic agent/ OR exp interleukin 17/ OR exp tumor necrosis factor inhibitor/ OR (antirheumatic agent OR biological disease-modifying anti-rheumatic drugs OR disease-modifying anti-rheumatic drugs OR DMARD OR TNF inhibitor OR anti-TNF OR tumor necrosis factor OR tumour necrosis factor OR TNF-alpha OR TNF-a OR TNF-antagonist).ti,ab.
#2	Exp adalimumab/ or exp certolizumab pegol/ or exp etanercept/ or exp golimumab/ or exp infliximab/ or exp secukinumab/ or exp ixekizumab/ or (adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade OR secukinumab OR Cosentyx OR AIN457 OR ixekizumab OR taltz OR LY2439821 OR LY-2439821).ti,ab. OR (exp biosimilar agent/ AND (TNF inhibitor OR anti-TNF OR tumor necrosis factor OR tumour necrosis factor OR TNF-alpha OR TNF-a OR TNF-antagonist).ti,ab.)
#3	(ankylos$ OR spondyl$ OR spondyloarthropath$ OR spondylarthropath$ OR spondylarthrit$ OR Bechterew$ disease OR Marie-Struempell$ disease OR rheum$ spondylitis OR axial SpA).ti,ab.
#4	(1 OR 2) AND 3
#5	4 AND random$.ti,ab.
#6	review.pt. not (((systematic or meta) and analy$) or ((indirect or mixed) and treatment comparison)).ti,ab.
#7	5 NOT 6
#8	Limit 8 to (English language and yr=”2019-current”)

1.7.3 CENTRAL search strategy

Table 46: October 2020 SLR update – CENTRAL search string

#	Search terms
#1	exp Antirheumatic Agents/ OR exp Interleukin-17/ OR (biological disease-modifying anti-rheumatic drugs OR disease-modifying anti-rheumatic drugs OR disease modifying antirheumatic drug$ OR DMARD$ OR TNF inhibitor$ OR anti-TNF OR tumor necrosis factor$ OR tumour necrosis factor$ OR TNF-alpha OR TNF-a OR TNF-antagonist).ti,ab.
#2	exp adalimumab/ or exp certolizumab pegol/ or exp etanercept/ or exp golimumab/ or exp infliximab/ or exp secukinumab/ or exp ixekizumab or (adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade OR secukinumab OR cosentyx OR AIN457 OR ixekizumab OR taltz OR LY2439821 OR LY-2439821).ti,ab. OR ((exp Biosimilar Pharmaceuticals/ OR biosimila$.ti,ab.) AND (TNF inhibitor OR anti-TNF OR tumor necrosis factor$ OR TNF-alpha OR TNF-a OR TNF-antagonist).ti,ab.)
#3	(ankylos$ OR spondyl$ OR spondyloarthropath$ OR spondylarthropath$ OR spondylarthrit$ OR Bechterew$ disease OR Marie-Struempell$ disease OR rheum$ spondylitis OR axial SpA).ti,ab.

#	Search terms
#4	(1 OR 2) AND 3
#5	4 AND random$.ti,ab.
#6	review.pt. not (((systematic or meta) and analy$) or ((indirect or mixed) and treatment comparison)).ti,ab.
#7	5 NOT 6
#8	Limit 7 to English language
#9	Limit 8 to yr=”2019-current”

1.7.4 Embase (via Ovid) conference search strategy

Table 47: October 2020 SLR update – conference search strategy

#	Search terms
#1	exp antirheumatic agent/ OR exp tumor necrosis factor inhibitor/ OR exp interleukin 17/ OR (antirheumatic agent OR biological disease-modifying anti-rheumatic drugs OR disease-modifying anti-rheumatic drugs OR DMARD OR TNF inhibitor OR anti-TNF OR tumor necrosis factor OR tumour necrosis factor OR TNF-alpha OR TNF-a OR TNF-antagonist).ti,ab.
#2	Exp adalimumab/ or exp certolizumab pegol/ or exp etanercept/ or exp golimumab/ or exp infliximab/ or exp secukinumab/ or exp ixekizumab/ or (adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade OR secukinumab OR Cosentyx OR AIN457 OR ixekizumab OR taltz OR LY2439821 OR LY-2439821).ti,ab. OR (exp biosimilar agent/ AND (TNF inhibitor OR anti-TNF OR tumor necrosis factor OR tumour necrosis factor OR TNF-alpha OR TNF-a OR TNF-antagonist).ti,ab.)
#3	(ankylos$ OR spondyl$ OR spondyloarthropath$ OR spondylarthropath$ OR spondylarthrit$ OR Bechterew$ disease OR Marie-Struempell$ disease OR rheum$ spondylitis OR axial SpA).ti,ab.
#4	(1 OR 2) AND 3
#5	4 AND random$.ti,ab.
#6	review.pt. not (((systematic or meta) and analy$) or ((indirect or mixed) and treatment comparison)).ti,ab.
#7	5 NOT 6
#8	limit 7 to english language
#9	American College of Rheumatology.cf,cg.
#10	eular.cf,cg.
#11	british society for rheumatology.cf,cg.
#12	ispor.cf,cg.
#13	OR/9-12
#14	8 and 14
#15	limit 15 to yr="2019 -Current"

1.7.5 Cochrane library

Table 48: October 2020 SLR update – Cochrane Database of Systematic Reviews (via Ovid) Search Algorithm

#	Search terms
#1	(antirheumatic agent OR interleukin-17 OR biological disease-modifying anti-rheumatic drugs OR disease-modifying anti-rheumatic drugs OR DMARD OR TNF inhibitor OR anti-TNF OR tumor necrosis factor OR tumour necrosis factor OR TNF-alpha OR TNF-a OR TNF-antagonist).ti,ab.
#2	(adalimumab OR Humira OR certolizumab OR cimzia OR CDP870 OR etanercept OR Enbrel OR 185243-69-0 OR golimumab OR Simponi OR infliximab OR Remicade OR secukinumab OR Cosentyx OR AIN457 OR ixekizumab OR taltz OR LY2439821 OR LY-2439821).ti,ab. OR (biosimilar.ti,ab. AND (TNF inhibitor OR anti-TNF OR tumor necrosis factor OR tumour necrosis factor OR TNF-alpha OR TNF-a OR TNF-antagonist).ti,ab.)
#3	(ankylos$ OR spondyl$ OR spondyloarthropath$ OR spondylarthropath$ OR spondylarthrit$ OR Bechterew$ disease OR Marie-Struempell$ disease OR rheum$ spondylitis OR axial SpA).ti,ab.
#4	(1 OR 2) AND 3
#5	Limit 4 to yr=”2019-current”

1.7.6 JAK Inhibitors and Bimekizumab

The SLR now incorporates JAK inhibitors and bimekizumab, and separate searches were run to identify studies reporting on the efficacy of these treatments. Search cutoff dates extend back to the original search window of the review, to ensure all overlap is captured (Table 49, Table 50, Table 51, Table 52, and Table 53)

Table 49: MEDLINE (via Ovid) Search Algorithm for JAK Inhibitor and Bimekizumab Update

#	Strategy
#1	exp Janus Kinase Inhibitors/ or ((janus adj kinase adj inhibitor*) or (JAK adj inhibitor*) or jakinibs).ti,ab.
#2	(tofacitinib or CP690550 or CP-690550 or Xeljanz or Jakvinus or tasocitinib or CP690550 or CP-690550 or upadacitinib or abt-494 or rinvoq or filgotinib or GLPG0634 or GLPG-0634 or GS6034 or GS-6034 or g146034 or g-146034 or bimekizumab or UCB4940 or UCB-4940).ti,ab.
#3	(ankylos$ OR spondyl$ OR spondyloarthropath$ OR spondylarthropath$ OR spondylarthrit$ OR Bechterew$ disease OR Marie-Struempell$ disease OR rheum$ spondylitis OR axial SpA).ti,ab.
#4	(1 OR 2) AND 3
#5	4 AND random$.ti,ab.
#6	review.pt. not (((systematic or meta) and analy$) or ((indirect or mixed) and treatment comparison)).ti,ab.
#7	5 NOT 6
#8	Limit 7 to English language
#9	Limit 8 to yr=”1991-current”

Table 50: EMBASE (via Ovid) Search Algorithm for JAK Inhibitor and Bimekizumab Update

#	Strategy
#1	exp Janus Kinase Inhibitor/ or ((janus adj kinase adj inhibitor*) or (JAK adj inhibitor*) or jakinibs).ti,ab,tn.
#2	exp filgotinib/ or exp tofacitinib/ or exp upadacitinib/ or exp risankizumab/ or (tofacitinib or CP690550 or CP-690550 or Xeljanz or Jakvinus or tasocitinib or CP690550 or CP-690550 or upadacitinib or abt-494 or rinvoq or filgotinib or GLPG0634 or GLPG-0634 or GS6034 or GS-6034 or g146034 or g-146034 or bimekizumzb or UCB4940 or UCB-4940).ti,ab.
#3	(ankylos$ OR spondyl$ OR spondyloarthropath$ OR spondylarthropath$ OR spondylarthrit$ OR Bechterew$ disease OR Marie-Struempell$ disease OR rheum$ spondylitis OR axial SpA).ti,ab.
#4	(1 OR 2) AND 3
#5	4 AND random$.ti,ab.
#6	review.pt. not (((systematic or meta) and analy$) or ((indirect or mixed) and treatment comparison)).ti,ab.
#7	5 NOT 6
#8	Limit 7 to English language
#9	Limit 8 to (article or article in press)
#10	Limit 9 to yr="1991-current"

Table 51: CENTRAL (via Ovid) Search Algorithm for JAK Inhibitor and Bimekizumab Update

#	Strategy
#1	exp Janus Kinase Inhibitors/ or ((janus adj kinase adj inhibitor*) or (JAK adj inhibitor*) or jakinibs).ti,ab.
#2	(tofacitinib or CP690550 or CP-690550 or Xeljanz or Jakvinus or tasocitinib or CP690550 or CP-690550 or upadacitinib or abt-494 or rinvoq or filgotinib or GLPG0634 or GLPG-0634 or GS6034 or GS-6034 or g146034 or g-146034 or bimekizumab or UCB4940 or UCB-4940).ti,ab.
#3	(ankylos$ OR spondyl$ OR spondyloarthropath$ OR spondylarthropath$ OR spondylarthrit$ OR Bechterew$ disease OR Marie-Struempell$ disease OR rheum$ spondylitis OR axial SpA).ti,ab.
#4	(1 OR 2) AND 3
#5	4 AND random$.ti,ab.
#6	review.pt. not (((systematic or meta) and analy$) or ((indirect or mixed) and treatment comparison)).ti,ab.
#7	5 NOT 6
#8	Limit 7 to English language
#9	Limit 8 to yr=”1991-current”

Table 52: EMBASE (via Ovid) Conference Search Algorithm for JAK Inhibitor and Bimekizumab Update

#	Strategy
#1	exp Janus Kinase Inhibitor/ or ((janus adj kinase adj inhibitor*) or (JAK adj inhibitor*) or jakinibs).ti,ab,tn.
#2	exp filgotinib/ or exp tofacitinib/ or exp upadacitinib/ or exp risankizumab/ or (tofacitinib or CP690550 or CP-690550 or Xeljanz or Jakvinus or tasocitinib or CP690550 or CP-690550 or upadacitinib or abt-494 or rinvoq or filgotinib or GLPG0634 or GLPG-0634 or GS6034 or GS-6034 or g146034 or g-146034 or bimekizumab or UCB4940 or UCB-4940).ti,ab.
#3	(ankylos$ OR spondyl$ OR spondyloarthropath$ OR spondylarthropath$ OR spondylarthrit$ OR Bechterew$ disease OR Marie-Struempell$ disease OR rheum$ spondylitis OR axial SpA).ti,ab.
#4	(1 OR 2) AND 3
#5	4 AND random$.ti,ab.
#6	review.pt. not (((systematic or meta) and analy$) or ((indirect or mixed) and treatment comparison)).ti,ab.
#7	5 NOT 6
#8	Limit 7 to English language
#9	American College of Rheumatology.cf,cg.
#10	eular.cf,cg.
#11	british society for rheumatology.cf,cg.
#12	ispor.cf,cg.
#13	OR/9-12
#14	8 and 13
#15	limit 14 to yr="2018 -Current"

Table 53: Cochrane Database of Systematic Reviews (via Ovid) Search Algorithm for JAK Inhibitor and Bimekizumab Update

#	Strategy
#1	((janus adj kinase adj inhibitor*) or (JAK adj inhibitor*) or jakinibs).ti,ab.
#2	(tofacitinib or CP690550 or CP-690550 or Xeljanz or Jakvinus or tasocitinib or CP690550 or CP-690550 or upadacitinib or abt-494 or rinvoq or filgotinib or GLPG0634 or GLPG-0634 or GS6034 or GS-6034 or g146034 or g-146034 or bimekizumab or UCB4940 or UCB-4940).ti,ab.
#3	(ankylos$ OR spondyl$ OR spondyloarthropath$ OR spondylarthropath$ OR spondylarthrit$ OR Bechterew$ disease OR Marie-Struempell$ disease OR rheum$ spondylitis OR axial SpA).ti,ab.
#4	(1 OR 2) AND 3
#5	Limit 4 to yr=”1991-current”

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Bimekizumab for treating axial spondyloarthritis [ID6245]

Professional organisation submission

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

1. Your name	BSR Spondyloarthritis (SpA) Special Interest Group (SIG)
2. Name of organisation	British Society for Rheumatology (BSR)
3. Job title or position	Chair of the BSR SpA SIG
4. Are you (please select Yes or No):	• An employee or representative of a healthcare professional organisation that represents clinicians? Yes • A specialist in the treatment of people with this condition? Yes • A specialist in the clinical evidence base for this condition or technology? Yes • Other (please specify):
5. Brief description of the organisation (including who funds it).	British Society for Rheumatology is the leading UK specialist medical society for health professionals working in rheumatology.
6. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	BSR receives funding from pharmaceutical manufacturers for our drug registers and for sponsorship of our annual conference and courses. We received £45,200 from UCB for our Annual Conference, and we also received funding from several of the comparators: AbbVie, Amgen, Celltrion Healthcare, Eli Lilly, Novartis, Pfizer, Sandoz and UCB pharma. Please enquire for exact funding amounts for comparators.
7. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

8. Is the technology clinically similar to the comparator(s)? Does it have the same mechanism of action, or a completely different mechanism-of-action? Or in what way is it different to the comparator(s)?	To some extent it is different from the comparators. Bimekizumab is a monoclonal IgG1 antibody that selectively inhibits 2 pro-inflammatory cytokines: interleukin (IL)-17A and IL-17F. Other IL-17 inhibitors licensed for axSpA only target IL17A (which can exist as a homodimer of two IL-17A chains or as a heterodimer with IL-17F). The dual specificity of bimekizumab against both IL-17A and IL-17F is novel.
9. If there are differences in effectiveness between the technology and its comparator(s) are these clinically meaningful?	The available data does not directly compare bimekizumab with other treatments for axSpA. At this stage there are no proven differences in effectiveness between bimekizumab and its comparators.
10. What impact would the technology have on the current pathway of care?	A relevant proportion of patients fail multiple targeted treatments. The availability of a new drug/mechanism of action has the potential to improve care for axSpA patients, particularly those that are refractory to other therapeutic options.
11. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care: rheumatology outpatient clinics.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The same principles of current care in NHS clinical practice will apply – the technology will add to the treatment options for people with axSpA.

13. Have there been substantial changes to the treatment pathway since the comparator appraisal that might impact the relevance of the comparator's appraisal?	No significant changes.
14. Overall, is the treatment likely to offer similar or improved health benefits compared with the NICE-recommended comparator?	Likely to offer similar improvements.
15. Do the clinical trials on the technology reflect current UK clinical practice?	In general, yes (obviously taking into account that trial populations are very selected groups of patients fulfilling long lists of inclusion/exclusion criteria).
16. Is the technology likely to affect the downstream costs of managing the condition (for example, does it affect the subsequent treatments)	Yes, having an effective treatment reduces individual and societal costs of axial SpA, improving quality of life and productivity. The effect of bimekizumab on subsequent treatments is not known.

17. Are there any potential equality issues that should be taken into account when considering this treatment? Consider whether these issues are different from issues with current care and why	No, there would not be any envisaged equality issues to be taken into account.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal
Bimekizumab for treating axial spondyloarthritis [ID6245]
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.

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About you

1.Your name	**Jill Hamilton**
2. Name of organisation	National Axial Spondyloarthritis Society
3. Job title or position	Head of Policy and Health Services
4a. Brief description of the organisation (including who funds it). How many members does it have?	NASS is the only charity in the UK solely dedicated to supporting people living with axial spondyloarthritis (axial SpA) including ankylosing spondylitis. We provide information and support to people with the condition, as well as campaigning for better treatment and care. NASS is funded by a variety of voluntary sources including membership, individual fundrasisers, charitable trusts, legacies and industry funding. We receive no statutory or government funding. NASS currently has 3,547 members, the majority of which have axial SpA (AS).
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.**	

UCB	Aspiring to Excellence QI programme	12,500.00
ABBVIE	Aspiring to Excellence QI programme	30,000.00
ELI LILLY	Aspiring to Excellence QI programme	30,000.00
NOVARTIS	NASS Members' Day & Annual General Meeting	26,486.00
NOVARTIS	All Party Parliamentary Group on Axial SpA secretariat	13,800.00
UCB	Patient Insights research recruitment and participation	6,160.00
UCB	Women of Childbearing Age Focus Group recruitment	440.00
NOVARTIS	Sex, Gender and Gender Identity research project	18,459.00
NOVARTIS	Advisory Fee for participation in UK POLC	675.00
ABBVIE	Speaker Fee - Back in Focus Event	400.00
JANSSEN	Core Funding	5,000.00
UCB	RHEUMACENSUS	660.00

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?	We have carried out several pieces of research, both to establish people's views on medication, and also their experiences of living with axial SpA.

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)?	N/A – we are unaware of anyone currently using bimekizumab**.**
7. Are there any key differences?	N/A
8. Will this technology be easier, the same, or more difficult to take than the comparator(s)? If so, please explain why	The technology will be slightly more difficult to use compared to some comparators which are administered using a pen.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	This is a new way of targeting axial spondyloarthritis which has not been used in the condition before, thereby increasing treatment option. Any drug that can improve the quality of life be available for people with axial SpA. All possible options for treatment be made available to patients to ensure the best possible care for everyone living with the condition. The impact that effective treatment could have on the wider economy is also importatn; if people are treated with the drug that suits them the best then they are more likely to be able to stay in work and contribute more fully to society.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	It is difficult to answer this question as we are not aware of anyone currently taking the technology.

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.	Yes – people with psoriasis for which it is already nice approved. Around 7% of people with axial SpA also have psoriasis.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• This is a new drug for treating axial SpA. • All drugs that could improve quality of life should be made available. • Being on the right medication can help to ensure that people are able to stay in work and contribute to wider society. • The drug is currently approved for plaque psoriasis; 7% of people with axial SpA will also have psoriasis. •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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External Assessment Group Report

Cost comparison evaluation process

Bimekizumab for treating axial spondyloarthritis

Produced by	Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE) Technology Assessment Group
Authors	Ruth Walker, Research Fellow, CRD Sumayya Anwer, Research Fellow, CRD Minyue Gao, Research Fellow, CHE Chinyereugo Umemneku-Chikere, Research Fellow, CRD Melissa Harden, Senior Information Specialist, CRD Ana Duarte, Research Fellow, CHE Sofia Dias, Professor of Health Technology Assessment, CRD
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Date completed	17/07/2023 (Updated 02/08/2023)

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Declared competing interests of the authors

None.

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Rider on responsibility for report

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

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Contributions of authors

Ruth Walker wrote the critique of the decision problem and safety evidence and contributed to the critiques of the systematic review, clinical effectiveness evidence and network meta-analyses. Sumayya Anwer contributed to the critiques of the decision problem, clinical effectiveness evidence and the systematic review and wrote the critique of the network meta-analyses. Minyue Gao contributed to the critique of the economic evidence, performed the cost-comparison model validation and the economic analyses. Chinyereugo Umemneku-Chikere contributed to the safety and discontinuation rates section, the quality assessment section and the critique of the network meta-analyses. Melissa Harden wrote the critique of the search strategies and provided editorial support. Ana Duarte contributed to the critique of the economic evidence and took overall responsibility for the economic section. Sofia Dias was project lead, supported the critical appraisal of the evidence and takes overall responsibility for the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined.

Table of Contents

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List of abbreviations

AE	Adverse event
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AxSpA	Axial spondyloarthritis
b/tsDMARD	Biologic and Targeted Synthetic DMARD
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
bDMARD	Biologic DMARD
BKZ	Bimekizumab
BNF	British National Formulary
CCG	Clinical Commission Group
CrI	Credible interval
CRP	C-reactive protein
CS	Company submission
CSR	Clinical study report
DMARD	Disease modifying anti-rheumatic drug
EAG	External Assessment Group
EMA	European Medical Assessment
ERG	Evidence review group
FE	Fixed effect
FTA	Fast track appraisal
HTA	Health technology appraisal
IBD	Inflammatory bowel disease
IL-17	Interleukin-17
IV	intravenous
IXE	Ixekizumab
MTA	Multiple technology appraisal
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient access scheme
Q4W	Every 4 weeks
RCT	Randomised controlled trial
RE	Random effect
SAE	Serious adverse event
SC	Subcutaneous
SEC	Secukinumab
SLR	Systematic Literature Review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment Emergent Adverse Event
TNF	Tumour necrosis factor
UK	United Kingdom
US	United States of America

EXTERNAL ASSESSMENT REPORT: COST COMPARISON EVALUATION PROCESS

1 EXECUTIVE SUMMARY

The External Assessment Group (EAG) agrees that this topic may meet the criteria for a cost-comparison approach as bimekizumab (BKZ) is being proposed for use at the same line of therapy, and is expected to have similar efficacy, to existing interleukin (IL)-17 inhibitors. However, currently available evidence on comparative efficacy of BKZ is limited and results for comparative efficacy and safety, both in the short- and long-term, are uncertain. Further details on key issues and areas of uncertainty are given below.

There was a delay in receiving some company documents and files in response to clarifications and the EAG has not been able to fully review them or carry out additional analyses. We have noted in the report where this may have hindered full consideration of the company's responses or additional analyses (Sections 4.2.3.4, 4.2.3.7 and 5.2.2).

1.1 Pathway position and comparators

Clinical advice to the EAG is that tumour necrosis factor (TNF)-α inhibitors are typically the first choice for adult patients with active axial spondyloarthritis (axSpA) Therefore, BKZ would most likely be used as a second-line option for patients who had a primary non-response to TNF-α inhibitors (that is, who failed to respond to treatment) and as a third-line option for patients who lost response to a second TNF-α inhibitor (after an alternative TNF-α inhibitor was tried at second-line). In this positioning, the EAG considers the most relevant comparator to be secukinumab (SEC) 150 mg, as this has a greater market share for non-radiographic-axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS) patients. This contrasts with the company's proposed most relevant comparator, ixekizumab (IXE), which the EAG believe is less used than SEC 150 mg at this line of therapy.

1.2 Similar effectiveness relative to selected comparators

The EAG considers non-inferiority between BKZ and SEC 150 mg or IXE plausible based on the evidence presented, albeit caveated by a number of uncertainties. The company submission (CS) presented network meta-analyses (NMAs) which showed no evidence of differences between BKZ and SEC 150 mg or IXE in patients with nr-axSpA and AS who were biologic/targeted synthetic disease modifying anti-rheumatic drug (b/tsDMARD)-naïve (or populations of predominantly b/tsDMARD-naïve patients), or in AS patients who were b/tsDMARD-experienced for the majority of outcomes. For some outcomes evidence suggested that BKZ may have better efficacy than the

comparators. However, estimates of comparative effectiveness are uncertain due to few trials and small numbers of patients included (particularly in the AS b/tsDMARD-experienced population), and all estimated credible intervals are wide. A network meta-analysis could not be conducted for nr-axSpA b/tsDMARD-experienced patients due to these patients not being included in the clinical trials. Therefore, there is no evidence of comparative efficacy between BKZ, SEC 150 mg and IXE, for this sub-population. A similar lack of evidence has been noted in previous appraisals.

Given that b/tsDMARD-experienced patients would be amongst those most likely to receive BKZ in clinical practice, the EAG consider the lack of reliable comparative evidence for these patients a key area of uncertainty.

1.3 Similarity of costs across interventions

Assuming clinical effectiveness and safety are similar between BKZ and comparators (SEC and IXE), all costs except those associated with drug acquisition are similar. Thus, differences in costs are solely driven by the prices of the drugs to the NHS, which are all confidential. Costs across interventions are compared in the confidential appendix to this external assessment report.

The robustness of the results of the cost comparison analysis may be affected by the areas of uncertainty highlighted in Sections 1.4, 1.5, 1.6 and 1.7. The EAG also notes that the appropriateness of assessing the cost-effectiveness of BKZ using a cost comparison analysis relies on the validity of the assumption of equivalent efficacy and safety to at least one relevant comparator, which is uncertain.

1.4 Primary treatment response

The cost-comparison analysis assumes primary treatment response is equivalent between BKZ and comparators, but this parameter is informed in the economic model by BKZ trial data. The EAG would have preferred this parameter to be informed by pooled evidence for BKZ, SEC 150 mg and IXE (by population and prior b/tsDMARD exposure subgroup). This approach would have allowed the use of all existing evidence and would be in line with the assumption of equivalent efficacy across treatments that underpins the cost-comparison analysis. It would also have allowed performing subgroup cost-comparison analyses by prior b/tsDMARD exposure.

1.5 Long-term efficacy

Due to the limitations in long-term data, the long-term efficacy of BKZ in axSpA is uncertain.

1.6 Long-term discontinuation

The longest followed up time reported in the CS on the use of BKZ by axSpA patients was 52 weeks (BE MOBILE 1 and BE MOBILE 2). However, patients' exposure to BKZ was reported up to 156 weeks (BE AGILE and BE AGILE 2). With the long-term use (up to week 156) there was an increase in the treatment emergent adverse events (TEAEs) reported. The EAG considers there is uncertainty regarding the long-term discontinuation probability for BKZ because of the lack of longer-term data.

Furthermore, there is uncertainty on whether the discontinuation probabilities applied in the model are reflective of treatment adherence in UK clinical practice, as evidence sources for these parameters are outdated and the company did not identify alternative values from more appropriate data sources. The EAG notes that the impact of uncertainty on treatment discontinuation (due to lack of primary response, Section 1.4, or loss of treatment effect or tolerability) can only be fully accounted for by modelling treatment sequencing in the context of a cost-utility framework. Thus, this uncertainty cannot be explored in the cost-comparison evaluation process, which is a limitation.

1.7 Time horizon

The most relevant time horizon for the cost comparison analysis is unclear due to uncertainty regarding the predicted duration of treatment with BKZ and the comparators. The mean treatment duration for each population and subgroup is determined by the proportion of patients who achieve primary treatment response (Section 1.4) and the long-term discontinuation probability (Section 1.6). While the magnitude of cost differences between BKZ and comparators for both the EAG and company's base case results is sensitive to this parameter when confidential PAS prices are considered for all treatments, the interpretation of the results as cost saving or cost increasing does not change over a time horizon value range from 1 to 10 years.

2 BACKGROUND

The company's justification for considering BKZ for the cost-comparison approach is based on BKZ being an alternative to existing technologies recommended by NICE for nr-axSpA and AS patients whose condition is not well controlled with non-steroidal anti-inflammatory drugs (NSAIDs), at the same place in the treatment pathway, and with a similar mechanism of action.

The company are claiming similarity or superiority in efficacy and similarity in safety compared to IXE which is the company's chosen comparator treatment, which was considered the most relevant treatment by the company, claiming that BKZ and IXE have equivalent affinity for binding to IL-17A in vitro. However, the EAG note that in-vitro results do not often translate into clinical practice and there is no evidence for this within the clinical trial evidence.

The company claim that IXE is most likely to be displaced by BKZ and use this as justification for choosing IXE as the most relevant comparator in this appraisal (CS, Section B.1.1.1). The company have also included evidence for comparison to SEC 150 mg and SEC 300 mg, but they were not considered the most relevant comparator, despite estimates of market share being higher for SEC 150 mg in both the nr-axSpA and AS populations (see Section 3.2).

The company claims similarity in administration, monitoring, disease management, and adverse event (AE) costs compared to IXE and SEC and therefore includes only drug acquisition costs in the cost-comparison model. Based on this, the company claims either cost savings (compared to IXE and SEC 300 mg) or similar costs (compared to SEC 150 mg) for both the nr-axSpA and AS populations.

The company provided a description of the disease area and the treatment pathway in Section B.1.3 of the CS and a general overview of the disease axial spondylarthritis (axSpA), the diagnosis and the clinical differences between the two subtypes (nr-axSpA and AS). The company also described the burden associated with the disease (clinically, humanistic, and economic), as well as the extra-articular and peripheral manifestations.

The company stated that the treatment pathway for both subtypes (AS and nr-axSpA) is similar based on current NICE recommendations. The company's clinical advisory board experts [redacted].[1] Clinical advice to the EAG supports this. However, the EAG's clinical advisers noted that Figure 1 in the CS describing the treatment pathway, should also include SEC as a first line biologic option for patients with nr-axSpA, although in most cases a TNF-α inhibitor would be the first biologic offered to both AS and nr-axSpA patients, unless there are contraindications.

Bimekizumab is a humanised IgG1/κ monoclonal antibody that selectively inhibits both IL-17A and IL-17F. It is delivered by subcutaneous (SC) injection via a pre-loaded pen or syringe every four weeks. The company postulate that BKZ would provide greater clinical response (resolution of inflammation) in IL-17 mediated disease than IL-17A inhibitors alone (SEC and IXE) by neutralizing both IL-17A and IL-17F. However, the added benefit of the additional IL-17F inhibitor for axSpA is unknown and there is no clinical trial data to support this claim. Clinical advice to the EAG is that this would make no meaningful difference to axSpA symptoms, compared to other IL-17A inhibitors, which is [redacted].

BKZ has been authorised by the EMA for moderate to severe plaque psoriasis, psoriatic arthritis, and axial spondyloarthritis.[2] In the UK, NICE has recommended BKZ for severe plaque psoriasis.[3]

2.1 Summary of the EAG's view

The EAG believes that BKZ has a similar mechanism of action to other IL-17 inhibitors used for axSpA. Despite the addition of IL-17F inhibitor to BKZ compared to IL-17A inhibitors such as SEC and IXE, there is no evidence suggesting that this difference translates into increased clinical response with BKZ.

3 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

3.1 Population

The final scope issued by NICE covers all adults with active axSpA. The population addressed in the company submission aligns with the NICE recommendations for the company's chosen comparator treatment, IXE, and therefore covers adults with active nr-axSpA or AS that is not controlled well enough with conventional therapy and/or NSAIDs and where TNF-α inhibitors are not suitable or do not control the condition well enough. Clinical advice to the EAG supported this positioning noting that this population is broadly representative of patients who would receive the intervention in practice. The EAG therefore considers this population to be suitable.

However, some patients with active axSpA, may not be suitable for treatment with BKZ. Contraindications for BKZ detailed in the company submission include patients with clinically significant active infections, including active tuberculosis. The European medical agency (EMA) has also advised that BKZ may increase the risk of infections such as upper respiratory tract infections and oral candidiasis, and it should be used with caution in patients with chronic infection or a history of recurrent infection. In addition to these contraindication, clinical advice to the EAG is that BKZ, as with other IL-17 inhibitors, would be used cautiously in patients with inflammatory bowel disease (IBD). Patients with previous and active IBD would not be given BKZ, and clinicians may also opt not to give it to patients with a known family history of the condition.

In response to clarification questions, the company confirmed that BKZ is not recommended in patients with IBD and if a patient develops signs and symptoms of IBD or experiences an exacerbation of pre-existing IBD, BKZ should be discontinued, and appropriate medical management initiated. It is estimated that IBD affects ~5% of patients with axSpA[4] and therefore these patients, along with those at risk of the condition would likely not be suitable to receive the intervention in practice. However, clinical advice to the EAG was that patients presenting with axSpA are not routinely screened for IBD (apart from being asked about compatible symptoms, and referral to gastroenterology for further assessment accordingly), therefore it is mostly those patients presenting

with IBD symptoms who would be offered an alternative to IL-17 inhibitors. Overall, contraindications for treatment with BKZ are consistent with other IL-17 inhibitors.

Treatment decision may also be dependent on other extra-articular symptoms. Patients presenting with psoriasis (affecting ~10% of axSpA patients[4]), would be more likely to receive an IL-17 inhibitor earlier in the treatment pathway, as there is evidence that this class of biologics are effective at treating this symptom. Table 1 summarises the clinical decision-making for positioning of BKZ and other IL-17 inhibitors.

Table 1. EAG clinical adviser opinions on comparator use and the anticipated use of bimekizumab.

Subpopulation or subgroup of nr-axSpA and AS* patients	**EAG clinical advisers' opinions on:**	
	The comparators most likely to be used	**The anticipated use of bimekizumab**
b/tsDMARD-naïve	TNF-α inhibitors, namely, adalimumab or etanercept for most patients. In a smaller proportion of patients an IL-17A inhibitor may be considered.	Very unlikely to be used
b/tsDMARD-naïve and contraindicated for TNF-α inhibitors	Secukinumab, ixekizumab or upadacitinib	1st line**
No response to first b/tsDMARD (typically a TNF-α inhibitor)	Switch to another mode of action, i.e., to secukinumab/ ixekizumab or upadacitinib if previously on TNF-α inhibitor.	2nd line or later (Most likely 2nd line)
Responded to first b/tsDMARD (a TNF-α inhibitor) but lost response later	Either try another TNF-α inhibitor or switch to secukinumab/ ixekizumab or upadacitinib	2nd line or later (Most likely 3rd line)

* Clinical advice to the EAG was that treatment approaches would be similar for nr-axSpA and AS patients. **Clinical advice to the EAG was that very few patients are contraindicated to TNF-α inhibitors
Abbreviations: AS, ankylosing spondylitis; b/tsDMARD, biologic/targeted synthetic disease modifying anti-rheumatic drug; EAG, external assessment group; IL, interleukin; nr-axSpA, non-radiographic axial spondyloarthritis; TNF, tumour necrosis factor.

3.2 Comparators

The company propose BKZ would be used as a first line therapy for TNF-α inhibitor contraindicated patients who were b/tsDMARD-naïve, or second line and later for all other patients (b/tsDMARD-experienced). In this positioning, they consider the most relevant comparator for BKZ to be the IL-17A inhibitor IXE in both the nr-axSpA and AS populations. This is justified by claims that IXE is the most similar treatment to BKZ in terms of efficacy and safety and that the evidence for SEC is more heterogeneous with both 150 mg and 300 mg doses being in use and trials reporting results for SEC administered by intravenous (IV) induction rather than the SC administration of SEC in clinical practice.

However, clinical advice to the EAG is that IXE and SEC have similar efficacy, although IXE may lead to more injection site reactions, so SEC 150 mg is usually preferred with the 300 mg dose being rarely used for axSpA (it is mainly used for TNF-α inhibitor experienced patients with psoriatic arthritis). The EAG's clinical advisers also noted that the mode of administration (IV loading doses in randomised controlled trials (RCTs), versus SC only in clinical practice) should not make a difference to the efficacy of SEC. In the company's cost-comparison, results are presented for comparisons to IXE, SEC 150 mg and SEC 300 mg.

The EAG believes that SEC 150 mg is the most relevant comparator as it has a higher market share than IXE at the company's current positioning. Clinical advice to the EAG was that in the positions of second-line (for patients who had a primary non-response to TNF-α inhibitors) and third-line (for patients who lost response to an TNF-α inhibitors at second line) in the treatment pathway, SEC is the most commonly used IL-17 inhibitor in clinical practice and was expected to have the greater market share for nr-axSpA and AS patients compared to IXE. This is based on clinical experience of SEC being more efficacious than IXE, and adverse injection site reactions associated with IXE, which can cause patients to have poor adherence and/or discontinue this medication.

Furthermore, the EAG had access to axSpA prescription data from the Cambridgeshire and Peterborough Clinical Commissioning Group (CCG) (with a patient population of 967,307 people in 2018[5]), which suggested no use of IXE in the b/tsDMARD-naïve (1.7% for SEC) and a higher use of SEC compared to IXE in the b/tsDMARD-experienced (25.0% vs 13.2%) *(personal communication via email with Deepak Jadon, 22nd June 2023)*. The EAG notes that the data do not distinguish between AS and nr-axSpA, as this information is not always recorded clearly, and that the data holder cautioned that there may be inaccuracies due to records not always being updated when treatment is discontinued or patients no longer being registered with the CCG *(personal communication via email with Deepak Jadon, 22nd June 2023).* Additional prescription data from the Hertfordshire and West Essex Integrated Care Board (with a patient population of approximately 1.5 million people)[6] supported this, with no use of IXE as a first line therapy in both the AS and nr-axSpA b/tsDMARD-naïve populations (4% of 616 prescriptions and 1% of 83 prescription in SEC, respectively) and a higher use of SEC at second line therapy in both the AS and nr-axSpA experienced populations (24.45% in SEC and 0.55% in IXE of 182 prescriptions and 25% in SEC and 0% in IXE of 8 prescriptions respectively. Despite their limitations, these data support the EAG's assertion that SEC has a higher market share than IXE.

The company have also submitted a 2022 market share analysis[7] which was informed by [redacted]. The results of the analysis are summarised in

Table 2 (results extracted by the EAG from the Excel spreadsheet submitted by the company), and suggest that TNF-α inhibitors have the highest market share overall in axSpA, and at treatment initiation and switch (terms used by the company and which seem to refer to first line and subsequent lines of treatment, respectively). The market share analysis also suggest that SEC has a substantial market share at subsequent lines of treatment for the full axSpA population (28.4%) and for the subpopulation for whom TNF-α inhibitors are contra-indicated (61.5% at first line and 48.7% for subsequent lines of treatment).

Table 2. Market share distribution estimated by the company

Market share	All axSpA			axSpA TNF-α inhibitors contraindicated*		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Despite the results of the market share analysis, the company further justify not using SEC as the main comparator treatment due to "*substantial off-label use"* of SEC 300 mg in the UK and US (Section B.1.1.1, CS). However, the EAG do not agree that this is a valid reason to dismiss SEC 150 mg as a comparator. While the market share analysis[7] provided by the company [redacted], the company has provided estimates for the proportion of patients receiving SEC 300 mg in clinical practice. The EAG notes these estimates are based on market research conducted in the UK,[8, 9] but the methodology used in one of these references was not provided by the company,[9] and therefore, could not be validated by the EAG. The company also presented observational data[10-12] (company's response to clarification question A1) as supporting evidence for the use of SEC 300 mg. Given that these studies refer to the use of SEC in other jurisdictions, the EAG consider these unlikely to be relevant to the UK.

The EAG also notes that

i) SEC 300 mg is not recommended by NICE for AS or nr-axSpA (although 300 mg is an option only for AS, according to the British National Formulary (BNF)[13] and this is in line with the European summary of product characteristics (SmPC).[2]

ii) the company's budget impact analysis suggests a higher proportion of patients treated with SEC 150 mg compared to IXE, and

iii) clinical advice to the EAG was that SEC 300 mg is only used by some patients (for example, if they do not have primary response to the 150 mg dose or due to having a weight higher than 90 kg). The company's own advisory boards estimated that [redacted][1] [redacted].

Given the data and advice provided to the EAG and data provided by the company in their budget impact analysis showed [redacted], the company were asked to further clarify their decision to choose IXE as the main comparator in this appraisal. Their justification was centred on IXE being most similar to BKZ in terms of efficacy and safety and being the most likely treatment to be displaced by BKZ, as opposed to SEC which is a more established treatment with a higher market share. However, the EAG do not agree that these are valid reasons to select a comparator treatment within the cost-comparison approach.

3.3 Outcomes

The company have included most of the outcomes in the NICE final scope, with the exception of the peripheral symptom of dactylitis, stating this is due to dactylitis not being a core manifestation. The EAG notes that this symptom has been addressed in the previous appraisals of SEC for AS, TA407,[14] but not in other appraisal of key chosen comparators e.g., SEC for nr-axSpA (TA719[15]) and IXE for AS (TA718[16]). The EAG requested outcome data for additional peripheral symptoms at clarification stage, as this was not available in the company submission. The company responded with data at baseline, 16 and 52 weeks for the peripheral symptom, enthesitis-free state (Table 3 in the company's response to clarifications question A5) but confirm that data for dactylitis and peripheral arthritis were not collected past baseline.

The incidence of psoriasis has only been provided at baseline and the EAG requested data on this outcome at 16 and 52 weeks at the clarification stage. However, the company confirmed these are not available.

3.4 Subgroups

The company have addressed the subgroups included in the NICE final scope by providing clinical trial evidence for patients with AS and nr-axSpA who are a) b/tsDMARD-experienced and b) b/tsDMARD-naïve (see Section 4.2.2.1). However, there is a lack of patients with nr-axSpA who are b/tsDMARD-experienced within the clinical trial populations and given these patients would be amongst those most likely to receive BKZ in clinical practice, the EAG consider this a key area of

uncertainty. Furthermore, the cost-comparison analysis does not present subgroup results by prior b/tsDMARD exposure.

3.5 Summary of EAG's view

Clinical advice to the EAG was that a new treatment option within the IL-17 inhibitor class would be very welcome by patients and the clinical community, due to issues with persistence of SEC which often loses efficacy around 12-18 months and the more common adverse injection site reactions to the alternative IL-17 inhibitor IXE. The EAG's clinical advisers noted that their current preferred IL-17 is SEC 150 mg, although they would consider BKZ as an alternative, if this was available.

In addition, we note that:

- BKZ would most likely be used as a second-line treatment for patients who had a primary non-response to TNF-α inhibitors and third-line for patients who lost response to TNF-α inhibitors, in place of an existing IL-17 inhibitor.
- The EAG disagrees with the choice of the IL-17 inhibitor IXE as the main comparator. The IL-17 inhibitor SEC 150 mg is a more appropriate comparator as clinical advice to the EAG is that it is most commonly used in the proposed positioning for axSpA.
- Comparative efficacy data is lacking for the nr-axSpA b/tsDMARD-experienced population, a subgroup of interest in the NICE scope. Given these patients would be amongst those most likely to receive BKZ in clinical practice, the EAG consider this a key area of uncertainty.

4 SUMMARY OF THE EAG'S CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

The company carried out a systematic literature review (SLR) to identify evidence on the effectiveness of BKZ compared to other available interventions for axSpA.

4.1 Systematic review

4.1.1 Search strategy

Initially search strategies were found to be missing from Appendix D of the company submission. This was raised by the EAG at the clarification stage and in response the company provided all search strategies and confirmed that the April 2022 update searches were included in two additional NMA reports.[17, 18]

The most recent update searches in January 2023 and April 2022 were found to be fit for purpose overall and are likely to have identified relevant published or unpublished studies during the period 1st January 2020 – 10th January 2023.

The original search strategies from May 2012 and subsequent update searches (Oct 2013, July 2014, Jan 2017, April 2018, April 2019 and October 2020) contained flaws and were not considered to be consistent with current guidance or best practice for comprehensive searching to identify studies for a systematic review. Therefore, it is more likely that studies would have been missed by these earlier searches. The EAG made attempts to check that the submission had identified all relevant trials by comparing them to the studies identified in previous NICE appraisals in nr-axSpA and AS. More details are included in Section 4.2.3.5.

Further details of the EAG critique of the searches can be found in Table 3.

Table 3. EAG appraisal of company searches

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	PARTLY	Search strategies for the most recent update of the clinical SLR (Jan 2023) only were provided in Appendix D of the company submission. Although the reporting of these searches was clear and comprehensive, the original searches (May 2012) and subsequent update searches (x6) were missing. All requested search strategies were provided by the company in their response to clarifications. However, reporting was poor with numbers of hits per search line missing for most strategies, several search dates reported looked to be incorrect and details of the database providers were missing. The April 2022 search strategies were found in additional NMA reports submitted by the company.[17, 18] The reporting of these searches was clear and comprehensive. The NMA reports were not referenced in Appendix D.
Were appropriate sources searched?	PARTLY	Comprehensive range of databases, trial registers, conferences, and health technology assessment (HTA) agency websites were searched. Limited searching for previous systematic reviews.
Was the timespan of the searches appropriate?	YES	Taking all of the searches together they cover the period 1991 to 10th January 2023.
Were appropriate parts of the PICOS included in the search strategies?	YES	Radiographic/non-radiographic axial spondyloarthritis [Population] AND Bimekizumab [Intervention] OR various comparators (including SEC and IXE) [Comparators] AND RCTs [Study design]
Were appropriate search terms used?	YES	April 2022 and Jan 2023 update searches.
	PARTLY	May 2012 search and updates (Oct 2013, July 2014, Jan 2017, April 2018, April 2019 and October 2020) – missing some subject heading searches and free text search terms.
Were any search restrictions applied appropriate?	NO	Searches were limited to English language articles, therefore language bias is possible.

Were any search filters used validated and referenced?	PARTLY	April 2022 and Jan 2023 update - Scottish Intercollegiate Guidelines Network (SIGN) study design search filters were used to limit to RCTs in MEDLINE and Embase. These filters were referenced but have not undergone external validation.
	NO	May 2012 search and updates (Oct 2013, July 2014, Jan 2017, April 2018, April 2019 and October 2020) – validated RCT filters not used. Studies were only retrieved if they had the word random, randomised or randomized in the title or abstract. This is an inadequate way of searching for RCTs and could have resulted in missing studies.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Abbreviations: EAG, external assessment group; IXE, ixekizumab; NMA, network meta-analysis; RCT, randomised controlled trials; SEC, secukinumab; SLR, systematic literature review.

4.1.2 Study selection and data extraction

The inclusion criteria are presented in Table 3 Appendix D of the CS and relate to study selection of the records identified in the April 2022 to January 2023 search update. All relevant interventions/comparators measures listed in the NICE scope were included. Studies including populations with mixed populations (i.e. both AS and nr-axSpA patients) in which outcomes for the subpopulations are not reported separately were excluded. The EAG feel these studies could have added supplementary evidence, considering BKZ will be used in both populations. Languages other than English were also excluded. Therefore, there may be relevant studies in non-English language that were not included in the evidence synthesis. The EAG considers remaining inclusion/exclusion criteria to be appropriate.

Although not explicitly excluded, extra-articular manifestations of uveitis, IBD and psoriasis are not listed in the review's inclusion criteria but are listed within the NICE scope. Clinical advice to the EAG was that decisions regarding which b/tsDMARD to offer are sometimes influenced by their likely impact on extra-articular manifestations. Therefore, the EAG notes that it may have been useful to identify any relevant clinical evidence that reported on these outcomes to facilitate comparison with other interventions used to treat AS/nr-axSpA.

Appropriate methods were used to select studies for inclusion and to reduce reviewer error and bias with two reviewers conducting the screening of literature independently and any discrepancies resolved through communication with each other and if needed the assistance from a third reviewer. Data extraction methods were also appropriate with one reviewer extracting the data and another checking the data extraction for accuracy.

The company state that a feasibility assessment was performed to determine which of the unique clinical trials identified by the SLRs (including the January 2023 update) (reported as 65 in the CS), could be included in the NMA (reported as 37 in the CS). However, the EAG could not locate the details on the methods of this feasibility assessment and therefore were unable to critique its conduct during the timelines of this appraisal.

4.1.3 Quality assessment

The methods of quality assessment are reported in Section D.1.6 Appendix D of the CS. The company used the minimum criteria recommended by NICE for assessment of risk of bias (which is the York Centre for Reviews and Dissemination 7 item checklist for RCTs) and generalisability in parallel group RCTs. Judgements for each criterion were reported with limited justification for these choices, and an overall risk of bias judgement for each study was not presented. Though it is stated that only RCTs were included in the SLR, in 12 studies it was unclear if patients were randomised or not. Out of the 37 studies included in the NMA, six studies could be regarded as having a high risk of bias because the majority of the items on the checklist were judged as unclear. No action beyond reporting the results of the quality assessment was taken for clinical studies of uncertain or high risk of bias. The EAG note the potential impact of bias on the clinical effectiveness and results as a limitation.

4.2 Clinical effectiveness of bimekizumab

Clinical effectiveness evidence on the use of BKZ to treat nr-axSpA and AS comes from two RCTs, BE MOBILE 1 and BE MOBILE 2 respectively, described in Section B.3.3 in the CS.

BE MOBILE 1 and BE MOBILE 2 were phase 3 RCTs comparing BKZ (160 mg/mL) to placebo. The primary endpoint for both trials was the number of patients with at least 40% improvement in the Assessment of SpondyloArthritis International Society scale (ASAS40) response at 16 weeks. According to the EAG's clinical advisors, while ASAS40 is commonly used in clinical trials, the number of patients with at least 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50) is the clinical benchmark for response employed in clinical practice in the UK.

The methodology for BE MOBILE 1 and BE MOBILE 2 is summarised in Table 8 (page 39) of the CS. A schematic for the design of the trials is provided in Figure 2 (page 38) of the CS. The clinical trials had a randomised-controlled period lasting 16 weeks, and an extended follow-up period where all patients were given BKZ, regardless of original treatment allocated, up to 52 weeks.

4.2.1 Clinical trial population

BE MOBILE 1 includes patients with nr-axSpA and BE MOBILE 2 includes patients with AS. Patients in both clinical trials had inadequate response to at least two NSAIDs or contradictions to

NSAIDs, and both studies compared BKZ to placebo. The percentage of b/tsDMARD-naïve population in BE MOBILE 1 and 2 were 89% and 84%, respectively.

The lack of clinical trial evidence in the b/tsDMARD-experienced group is a key limitation, given that in NHS clinical practice most patients would receive a TNF-α inhibitor as first-line of therapy, and most patients receiving an IL-17 inhibitor would be b/tsDMARD-experienced. Clinical advice to the EAG was that most patients with prior biologic experience are less responsive to subsequent lines of therapy which could be due to different reasons including an initial misdiagnosis, the immunomodulatory effect of the therapy affecting their response to subsequent therapies or patient characteristics that make their disease difficult to treat. As such, it is likely that the absolute treatment effects observed in the BE MOBILE 1 and 2 trials are greater than what would be observed in clinical practice for b/tsDMARD-experienced patients. However, it remains uncertain the extent to which the relative effect estimates (i.e. the effect of BKZ compared to placebo) may differ. Advice to the EAG was that the relative treatment effect would likely be lower for all b/tsDMARD-experienced patients, regardless of the biologic therapy that they receive at second line (see Section 4.2.2.1). The EAG also note that in the company's clinical advisory board [redacted].

The inclusion criteria for BE MOBILE 1 and 2 are reported in Table 7 of the CS. Clinical advice to the EAG was that the inclusion criteria for both trials are broadly appropriate and in line with those used in clinical trials of currently available treatments for this condition.

Baseline characteristics are reported in Table 13 of the CS. Clinical advice to the EAG was that the clinical trial population, represented approximately 30-40% of patients seen in NHS practice. In addition to the issues relating to the lack of biologic experienced patients, the trials include younger patients, with fewer comorbidities and higher baseline ASAS/BASDAI scores. The EAG further notes that the proportion of patients with extra-articular manifestations including IBD, uveitis and psoriasis are lower than is likely in practice,[19, 20] although BKZ would usually not be used in patients with IBD. The proportion of men in the clinical trial population is also higher than women, despite nr-axSpA in particular, affecting more women than men. These differences limit the applicability of the BKZ trial populations to an NHS setting. However, the EAG note that the BE MOBILE trial characteristics are broadly consistent with other clinical trials within nr-axSpA and AS including those of SEC 150 mg and IXE.[21-26]

The EAG also notes a high proportion of patients taking NSAIDs in both BE MOBILE 1 and 2. Data on the proportion of patients who remained on these therapies throughout the trial is not reported and therefore any impact this may have had on the efficacy results is unknown.

4.2.2 Clinical trial results

Efficacy results of the primary and secondary endpoints at 16 and 52 weeks for BE MOBILE 1 and 2 are reported in Section B.3.6.1- B.3.6.3 of the CS.

The company were asked to clarify the treatment effect estimates presented in Table 16 of the CS. Response to clarification suggests the majority of binary outcomes are reported as risk difference. However, the definition of some results remained unclear Therefore, the EAG have instead referred to Tables 8-1 in the clinical study report (CSR) week 24 interim analysis for BE MOBILE 1 and 2 which show results of primary and key secondary efficacy analysis based on the predefined sequential testing sequence at Week 16.

Of the outcomes considered in the cost-effectiveness analysis of previous appraisals (Table 4), BKZ showed significant improvements in mean change from baseline in BASDAI and Bath Ankylosing Spondylitis Functional Index (BASFI) scores, ASAS40 and ASAS20 compared to placebo in both BE MOBILE 1 and 2 at 16 weeks. For BASDAI50, the company presents only the number and proportion of patients achieving BASDAI50 at 16 weeks (both in the company submission and CSRs), noting the response rate was higher in the BKZ arm, indicating BKZ improves response compared to placebo.

In response to clarification, the company provided a table (Table 1 in the clarification response) summarising the extra-articular manifestations IBD and uveitis, at baseline, 16 and 52 weeks in BKZ and placebo arms. These data were also requested for psoriasis, but only the number at baseline were received (Table 2 in the clarification response). In AS the proportion of patients with IBD, increases with time on treatment, and is greater than placebo at 16 and 52 weeks, supporting the recommendations against using BKZ in patients at risk of, or with existing, IBD – see Section 3.1. In contrast, the number of patients developing uveitis was lower on the BKZ arm compared to placebo. Upon request, the company have also provided data at baseline, 16 and 52 weeks for the peripheral symptom, enthesitis-free state (Table 2 in the clarification response) but confirm that data for dactylitis and peripheral arthritis were not collected past baseline.

4.2.2.1 Subgroup analyses

The company conducted subgroup analyses based on prior TNF-α inhibitor exposure at week 16 for two outcomes: ASAS40 and Ankylosing Spondylitis Disease Activity Score (ASDAS) major improvement. The results for the subgroup analysis are presented in Table 20 in Section B.3.7.1 of the CS. In their response to clarifications, the company provided the results for subgroup analyses for an additional four outcomes: ASAS20, BASDAI50, and change from baseline in BASDAI and BASFI.

Due to the very small number of patients with prior TNF-α inhibitor exposure in BE MOBILE 1 and 2, the results for that subgroup are very uncertain (i.e., very wide 95% confidence intervals).

Therefore, the EAG agrees with the company that results for the subgroup analysis should be interpreted with caution. However, as this is a key subgroup of interest for this appraisal, this is a key limitation of the evidence.

4.2.3 Network meta-analyses

No RCTs directly comparing BKZ to other SEC or IXE in axSpA patients were available. Therefore, the company conducted a series of NMAs to obtain relative effects of BKZ compared to SEC and IXE using indirect evidence.

Previous appraisals in AS have conducted SLRs of RCTs to inform NMAs to evaluate the relative efficacy and safety of TNF-α inhibitors (TA383[27]), secukinumab (TA407[28]), ixekizumab (TA718[16]), and upadacitinib (TA829[29]) compared to other bDMARDs. Similarly, appraisals in nr-axSpA conducted NMAs to evaluate the relative efficacy and safety of TNF-α inhibitors (TA383[27]), secukinumab (TA719[30]), golimumab (TA497[31]), ixekizumab (TA718[16]), and upadacitinib (TA861[32]).

The methods used for NMA in this appraisal were broadly similar to the approaches used in previous appraisals. However, due to data sparsity for some subgroups and outcomes of interest, not all models were able to be fitted to all networks. A critique of the selected models is provided in Section 4.2.3.7.

4.2.3.1 Population

Previous appraisals in AS and nr-axSpA either conducted a single NMA on a mixed population which included both trials in b/tsDMARD-naïve and -experienced populations or modelled these populations separately.

In AS, TA718 and TA829 conducted separate NMAs on b/tsDMARD-naïve and b/tsDMARD-experienced populations, although the network for the b/tsDMARD-experienced population in TA829 did not include SEC or any TNF-α inhibitors. In TA718 sensitivity analyses which included trials where the population of interest was unclear or was mixed (naïve and experienced) were also conducted. TA383 and TA407 conducted a single NMA on a mixed b/tsDMARD population, with TA407 including a sensitivity analysis for the b/tsDMARD-naïve population only.

In nr-axSpA, there was insufficient evidence on b/tsDMARD-experienced populations, so NMAs were either conducted on a b/tsDMARD-naïve population (TA718 and TA719), or on a mixed population (TA383, TA497 and TA861). Typically, in trials with mixed populations, the majority of patients were b/tsDMARD-naïve. The EAG note that efficacy in the b/tsDMARD-experienced population would likely be lower than the overall estimate of treatment effect in BE MOBILE 1 and 2 due to these patients not responding as well to biological therapy compared to naïve patients.

In the current submission, for AS the company conducted NMAs on the b/tsDMARD-experienced population as well as two types of b/tsDMARD-naïve populations: the purely b/tsDMARD-naïve population (where all patients were b/tsDMARD-naïve), and the predominantly b/tsDMARD-naïve population (where >50% patients in a trial were b/tsDMARD-naïve). Due to the lack of data in the b/tsDMARD-experienced population in nr-axSpA, and consistent with previous appraisals, the company only conducted NMAs on the purely and predominantly b/tsDMARD-naïve populations.

As noted in Sections 1.1 and 3.1, the EAG believe that most patients receiving BKZ would have had at least one prior TNF-α inhibitor, therefore the most relevant population for the NMAs will be the b/tsDMARD-experienced population with the predominantly b/tsDMARD-naïve population being less relevant.

4.2.3.2 Timepoint of assessment of outcomes

There is a large amount of heterogeneity in the timepoint at which initial response was measured across trials included in the current and previous appraisals. The timepoint of assessment ranges between 10 to 16 weeks in the trials included in the current and previous NMAs. It has been suggested by evidence review groups (ERGs) in previous appraisals that this could introduce uncertainty to models. In particular, the ERGs in TA407 and TA718 discussed how response rates may be higher in trials where response is measured later, as patients would have a longer period to respond to their treatment. A summary of the timepoints assessed for previous appraisals is given in Table 6 in the Appendix.

In the NMAs presented in the current submission, outcomes were assessed at a pooled week 12-16 time point. If studies reported measurements at more than one timepoint in this time period, preference was given to 16-week data, provided no treatment cross-over had occurred by the later timepoint. This is in line with the timepoint of assessment used in the two BE MOBILE trials.

4.2.3.3 Selection of outcomes

NMAs were conducted for several outcomes, including some that were not considered in previous appraisals. Outcomes that were included in the cost-effectiveness or cost-comparison models in previous appraisals are presented in Table 4. The company's key outcomes (Table 4) are largely consistent with the key outcomes identified in previous appraisals. Results for the key outcomes and all additional efficacy outcomes are given in Sections B.3.9.3.1 - B.3.9.4.2 and in Appendix D of the company submission. The company also conducted NMAs for tolerability and safety outcomes. The two tolerability outcomes assessed were discontinuation due to any reason, and discontinuation due to AEs and the safety outcome was serious adverse events (SAEs). Results for the safety and tolerability outcomes are presented in Section B.3.9.5 and in Appendix D of the company submission.

Clinical advice to the EAG was that the most relevant outcomes to this appraisal are ASAS20, ASAS40, BASDAI50, change from baseline in BASDAI and BASFI and the tolerability and safety outcomes in Table 4. In this report we will focus on critiquing NMAs conducted for these outcomes.

Table 4. Key outcomes included in the bimekizumab appraisal and previous appraisals for ankylosing spondyloarthritis.

	BKZ (ID6245, this appraisal)	**TNF-αi (TA383[27])**	**IXE (TA718[16])**	**SEC (TA719[30])**	**SEC (TA407[28])**	**GOL† (TA497[31])**	**UPA† (TA829[29])**	**UPA† (TA861[32])**
Indication	AS; nr-axSpA	AS; nr-axSpA	AS; nr-axSpA	nr-axSpA	AS	nr-axSpA	AS	nr-axSpA
Key efficacy outcomes	ASAS20, ASAS40, BASDAI50, BASDAI CFB, BASFI CFB, BASMI CFB	BASDAI50, BASDAI CFB, BASFI CFB	BASDAI50, BASDAI CFB, BASFI CFB, long-term change in BASFI over time	BASDAI50, BASDAI CFB, BASFI CFB, Long-term change in BASFI over time	BASDAI50, BASDAI CFB, BASFI CFB, long-term change in BASFI over time	ASAS20, ASAS40, BASDAI50, BASMI CFB, BASDAI CFB, BASFI CFB	ASAS40, BASDAI50, BASDAI CFB, BASFI CFB,	ASAS40, BASDAI50, BASDAI CFB, BASFI CFB
Tolerability Outcomes	Discontinuation due to any reason, Discontinuation due to AEs							
Safety Outcomes	SAEs							

† There were no cost-effectiveness models in these appraisals as they were cost-comparisons.

Abbreviations: AE, adverse events; AS, ankylosing spondylitis; ASAS, assessment in spondyloarthritis international society; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis meteorology index; BKZ, bimekizumab; CFB, change from baseline; GOL, golimumab; IXE, ixekizumab; nr-axSpA, non-radiographic axial spondyloarthritis; SAE, severe adverse events; SEC, secukinumab; TNF-αi tumour necrosis factor-α inhibitors; UPA, upadacitinib

4.2.3.4 NMA models

The company fitted NMA models as recommended in the NICE Decision Support Unit Technical Support Documents 2, 3 and 4.[33-35]

At the clarification stage, the company provided additional details on the convergence and consistency checks performed. However, due to the late arrival of the NMA code and inputs, the EAG was unable to independently verify this.

Fixed-effect (FE, also termed common effect) models have been favoured by all previous appraisals, as summarised in Table 6 (in the Appendix). TA718, TA719, and TA497 only fit FE models. All remaining appraisals fit both fixed- and random-effects (RE) models but preferred the FE models for all outcomes. In this submission, the company fitted FE and RE NMA models. The model-type considered most appropriate by the company for each outcome is included in Table 7 in the Appendix.

Placebo-response adjustments have been explored in previous appraisals (Table 6 in the Appendix), but they were generally not considered appropriate, particularly when using RE models, due to data sparsity. In this appraisal the company explored placebo-adjustment in both FE and RE models although data sparsity means that RE placebo-adjusted models were not well estimated (95% credible intervals for the regression parameters were very wide and included zero – CS Appendix D, Supplement 1) and should be discarded.

As there are not many studies comparing IXE, SEC or BKZ, model assumptions imply that information on the between-study heterogeneity and the placebo-effect regression coefficient are primarily estimated from the evidence from trials conducted on TNF-α inhibitors. This is a limitation of the evidence base. In addition, most networks did not have loops formed of independent evidence sources so there it was not possible to check for inconsistencies between direct and indirect evidence. Where this was possible, the company's consistency checks found no evidence of inconsistency.

Class effect

During the appraisal for IXE in axSpA (TA718), the committee deemed it inappropriate to assume a class-effect for all biologic treatments and preferred not to assume equivalent efficacy across TNF-α inhibitors and IL-17A inhibitors.[16] However, this suggests that the assumption of similar clinical efficacy across IL-17 inhibitors may not hold, which contradicts the central assumptions made in this cost-comparison.

As the aim of this appraisal is to compare BKZ to IXE and SEC, and not to TNF-α inhibitors, using a class-effect to model TNF-α inhibitors would have no impact on the comparisons within the IL-17 inhibitor class.

4.2.3.5 Studies included in the NMA

Due to the structure of the networks, where most studies compare an active treatment to placebo, and most loops are formed by 3-arm studies, studies included in comparisons not involving BKZ, SEC or IXE will not have any impact on relative effect estimates of BKZ compared to SEC or IXE when FE NMA models are used, but will have some effect when placebo-adjusted models or RE models are considered. A list of studies included in NMAs for the EAG's outcomes of interest for BKZ, SEC, and IXE is presented in Table 8 in the Appendix.

The company did not include all trials that had been included in previous appraisals. In nr-axSpA, Barkham (2009),[36] which had been included in TA383, was excluded as the company considered that population was not relevant as patients needed to have MRI evidence of sacroiliitis (Table 69 in Appendix D of CS). In AS, Brandt (2003)[37] which had been included in TA718 and Van den Bosch (2002)[38] which had been included in TA829 and TA383 were not identified in the SLR conducted by the company.

The company also excluded Giardina (2010)[39] as it did not have a placebo control group. The EAG does not consider this a valid reason for exclusion as studies without a placebo control arm can still be included in NMAs that adjust for the placebo-effect. [40]

The EAG acknowledges that the addition of these trials would not have a direct impact on the comparison between BKZ and IXE/SEC. However, the inappropriate exclusion of studies adds to the EAG's critique of the company's SLR in Section 4.1.1.

For both AS and nr-axSpA, the evidence for BKZ and the comparators of interest is sparse, that is there are few studies per comparison, sample sizes are generally small and there is limited or no indirect evidence on the comparisons of interest. No comparator studies included in the company's network diagrams report data for all outcomes. In both AS and nr-axSpA, only one study provides data for IXE for each patient population. There was no evidence on SEC for BASDAI50 and change from baseline in BASFI for the b/tsDMARD-experienced AS population.

4.2.3.6 Potential causes of heterogeneity in the NMAs

The baseline characteristics for studies included in the NMAs for nr-axSpA and AS are given in Tables 11 and 13 in Appendix D of the CS, respectively. Overall, the majority of baseline characteristics are similar across studies. However, there is some variation in mean baseline C-reactive protein (CRP) levels across trials. The two BE MOBILE trials reported median baseline CRP values instead of the mean; the two measures are not directly comparable, but the median baseline CRP levels were lower than for the other studies (Tables 11 and 13, CS Appendix D).

The company's attempt to split the patient population by previous b/tsDMARD exposure may have mitigated some of the heterogeneity in the NMA. However, the use of the predominantly b/tsDMARD-naïve population as a proxy for the purely b/tsDMARD-naïve population (which would represent patients intolerant to TNF-α inhibitors receiving an IL-17 first-line) may introduce heterogeneity to the network. Although the use of a predominantly b/tsDMARD-naïve population is consistent with previous appraisals (Section 4.2.3.1), this may introduce heterogeneity and is a source of additional uncertainty.

The use of a pooled timepoint of assessment could also introduce heterogeneity in the NMA as patient response may vary depending on when they were assessed (Section 4.2.3.2). Heterogeneity in the quality of studies included in the NMA (Section 4.1.3) is also a limitation.

The earliest studies included in the NMA were from 2002. Changes in trial conduct and standard of care from then to now could add heterogeneity to the NMA.

4.2.3.7 Results presented in the company submission

The company present results for the predominantly b/tsDMARD-naïve population in both AS and nr-axSpA patients, claiming that the NMA results for these populations are more robust for all outcomes compared to the purely b/tsDMARD-naïve populations (which are included in Appendix D) due to having more studies included and larger sample sizes. The EAG agree that these are more robust analyses, however their result may be less generalisable in practice as they cover two sub-groups and studies contribute different proportions of b/tsDMARD-naïve and experienced patients none of which are likely to be aligned with the proportions in NHS clinical practice. On the whole, the EAG found the results for the purely bDMARD-naïve population to be consistent with the predominantly bDMARD-naïve population.

The company submission claims that IXE is the most similar IL-17 inhibitor to BKZ in terms of efficacy. NMA results for relevant outcomes suggest relative effects of SEC and IXE compared to BKZ are similar. However, the EAG believe that SEC 150 mg is the most relevant comparator as it is the most prescribed IL-17 inhibitor in the company's current positioning (see Section 3.2). Therefore, we will focus the critique on the comparative efficacy of BKZ to SEC 150 mg, whilst also commenting on the relative efficacy compared to IXE, where appropriate.

NMA model selection

For nr-axSpA, the company preferred FE models for all outcomes (Table 7 in the Appendix). The EAG agreed with all models selected by the company.

For the AS networks, the EAG did not always agree with the NMA model selected by the company. For ASAS20 in the b/tsDMARD-naïve population, the simpler placebo adjusted FE model fits the

data as well as the placebo-adjusted RE model selected by the company. Similarly, for the b/tsDMARD-experienced population, the EAG would prefer the FE models for both ASAS20 and change from baseline in BASFI, compared to the company's selection of the placebo-adjusted FE model, as the 95% credible interval (CrI) for the regression coefficient for the placebo-effect (beta) included 0 and was estimated with a lot of uncertainty. The company did not present the relative effect estimates from these models. Due to the late arrival of the NMA data and code, the EAG could not obtain these results independently. However, these estimates are unlikely to be meaningfully different from the treatment effects estimated by the company's preferred models.

nr-axSpA

For nr-axSpA, the results for the NMA for the predominantly b/tsDMARD-naïve population are reported in Tables 24 and 26 in the Appendix D of the CS. Results for the purely b/tsDMARD-naïve population are reported in Tables 23 and 25.

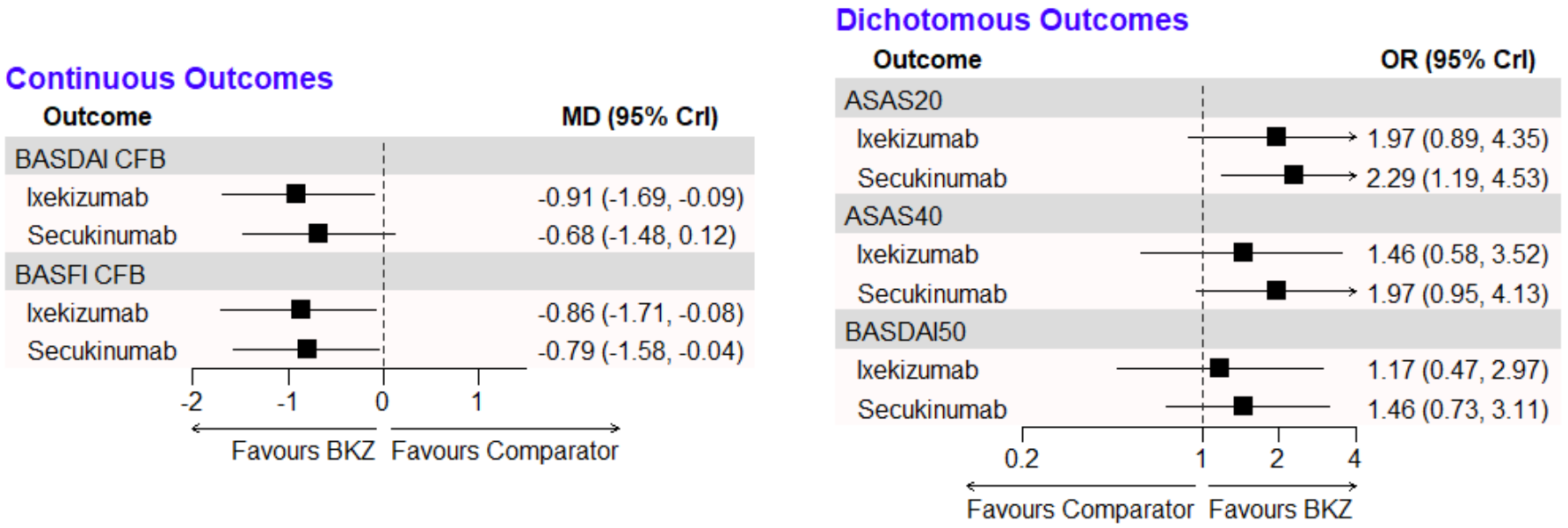
Treatment effect estimates comparing IXE and SEC to BKZ using the company's preferred NMA models for the outcomes used in previous appraisals are reported in Table 7 in the Appendix and presented visually in Figure 1. BKZ is favoured compared to IXE for both change from baseline in BASDAI and BASFI. Compared to SEC, BKZ is favoured for change from baseline in BASFI and ASAS20. For all other comparisons, the 95% CrI crosses the line of no effect.

AS

For AS, the results for the NMA of the predominantly b/tsDMARD-naïve population and b/tsDMARD-experienced populations are reported in Tables 28 and 30, Tables 31 and 32 in Appendix D of the CS, respectively. The results for the NMA of the purely b/tsDMARD-naïve population are reported in Tables 27 and 29 in Appendix D. Table 7 in the Appendix reports the treatment effect estimates comparing IXE and SEC to BKZ and these results are also shown in Figure 2. There is no evidence that BKZ is different from IXE or SEC for any of the important outcomes, as the 95% CrI for all estimates cross the line of no effect. However, these 95% CrIs are very wide and results are uncertain.

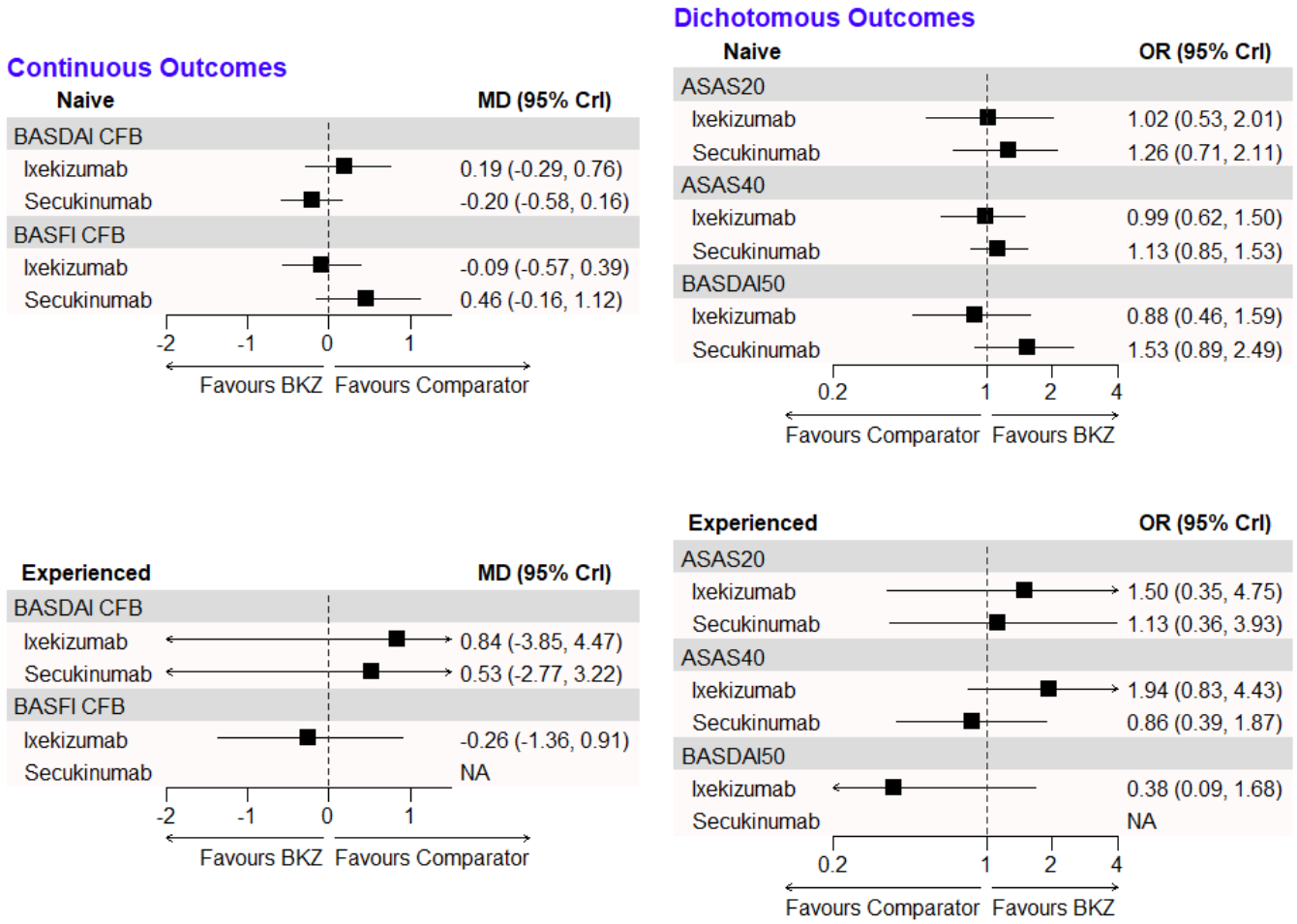
As there was no evidence for SEC for change from baseline in BASFI or BASDAI50 for the b/tsDMARD-experienced population, the treatment effect of BKZ could not be compared to SEC for these outcomes. The EAG note the lack of a comparison with SEC for BASDAI50 in particular, is a serious limitation as this is the outcome most commonly used to assess response in NHS practice, and the b/tsDMARD-experienced population is the most likely to receive BKZ and comparators in NHS clinical practice.

Figure 1. Treatment effect estimates for the company's preferred models for nr-axSpA (predominantly naïve network)



Abbreviations: BKZ, bimekizumab, CFB, change from baseline, CrI, credible interval; MD, mean difference; nr-axSpA, non-radiographic axial spondyloarthritis; OR, odds ratio.

Figure 2. Treatment effect estimates for the company's preferred models for AS



Abbreviations: AS, ankylosing spondylitis; BKZ, bimekizumab, CFB, change from baseline, CrI, credible interval; MD, mean difference; OR, odds ratio. NA, not available
Naïve is used to denote the predominantly b/tsDMARD-naïve population, and Experienced the b/tsDMARD-experienced population.

4.3 Safety of bimekizumab

Safety data is reported in Section B.3.10.1.1 of the company submission at 16 and 52 weeks. Clinical advice to the EAG was that BKZ, SEC and IXE have a broadly similar safety profile but that rates of candida infections may be higher in BKZ compared to IXE and SEC. This is reflected in available longer term clinical trial evidence for BKZ and comparators IXE and SEC, with rates of oral candidiasis at the end of treatment period being 0.9 % in SEC, at 104 week follow-up[26], 0% in IXE at 52 week follow-up[21] and [redacted] in BKZ in the BE MOBILE 1 and 2 trials, respectively at 52 weeks follow-up.[41, 42]

However, BKZ has been used in the BE AGILE and BE AGILE 2 for up to 156 weeks in the treatment of other conditions including axSpA. Use of the BKZ from 52 to 156 weeks increased the number of patients that reported TEAE (Appendix J in CS). Upper respiratory infection (especially nasopharyngitis) was the highest reported TEAE followed by oral candidiasis.

4.3.1 Discontinuation rates

Discontinuation rates at 16 weeks were broadly in line with those in clinical trials of SEC and IXE (Table 9 in the Appendix), although the EAG note, there may be difference in discontinuation rates between b/tsDMARD-experienced and -naïve populations.

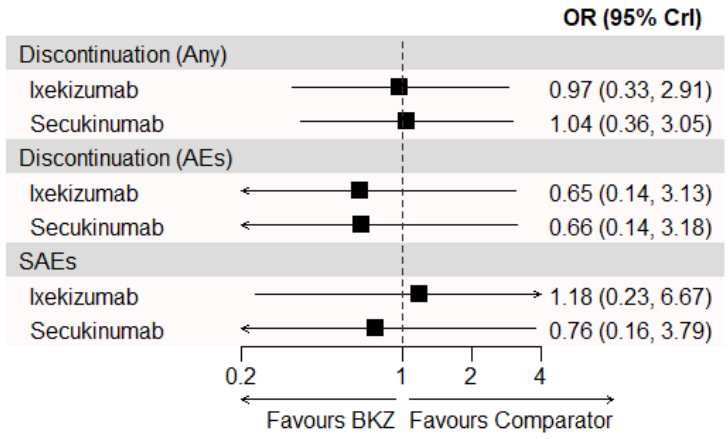
Evidence of longer-term discontinuation rates is available in the BE MOBILE 1 and 2 CSRs and show TEAEs leading to study discontinuation as [redacted] respectively, at the end of 52 weeks study period.[41, 42] Study discontinuations due to TEAEs are also available from the phase 11b open label BE AGILE study which shows from 0-48 weeks of those patients on 160 mg BKZ every 4 weeks 7 (4.7%) discontinued and from 48-156 weeks 14 (5.5%) discontinued.[43]

4.3.2 Network meta-analyses of safety and discontinuation outcomes

The company provide results for tolerability and safety until the 16 week point in the combined nr-axSpA and AS population in Section D.3.8.5 of Appendix D of the CS. The populations were combined due to data sparsity. The models preferred by the company and the resulting odds ratios are presented in Table 7 in the Appendix and in Figure 3.

Estimates for in discontinuations or in incidence of SAEs for BKZ compared to SEC or IXE are very uncertain as there are few discontinuation or serious adverse events in the trial populations. However, there is no evidence of differences between these treatments.

Figure 3. Results for NMAs conducted on safety and tolerability outcomes (combined axSpA safety population)



Abbreviations: AE, adverse events; BKZ, bimekizumab; CrI, credible interval; NMA, network meta-analysis; OR, odds ratio; SAE, serious adverse events

4.4 Summary of EAG's view

- The EAG considers that it is possible that BKZ, SEC 150 mg and IXE result in similar health outcomes, however limitations in the available evidence mean this is a key area of uncertainty.
- Estimates of comparative effectiveness for most outcomes in the AS and nr-axSpA b/tsDMARD predominantly naïve populations and particularly in the AS b/tsDMARD-experienced population, are uncertain due to few trials and small numbers of patients.
- There is no evidence comparing treatments in nr-axSpA b/tsDMARD-experienced patients but these patients would be amongst those most likely to receive BKZ in clinical practice. This is a key area of uncertainty in this appraisal.
- There was also a lack of evidence to compare BKZ to SEC for the outcomes BASDAI50 and change from baseline in BASFI for the b/tsDMARD-experienced population in AS, which is a key limitation.
- NMA estimates of discontinuation for any reason or for adverse events for the overall axSpA population were uncertain, but there was no evidence to suggest differences between BKZ, SEC or IXE.
- NMA estimates for serious adverse events for the overall axSpA population were uncertain, but there was no evidence to suggest differences between BKZ, SEC or IXE.

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

The appropriateness of assessing the cost-effectiveness of BKZ based on the results of a cost comparison analysis is underpinned by the assumption of equivalent efficacy (see Section B.3.9, CS) and safety (see Section B.3.10, CS) of BKZ to at least one relevant comparator. In the following sections, the EAG takes this assumption as valid, and aims to identify the set of assumptions under which BKZ is likely to be cost saving or equivalent in cost to the selected comparator. The EAG also highlights throughout the subsequent subsections, aspects of the cost comparison that may be affected by uncertainty surrounding the validity of assuming equivalent efficacy and safety of BKZ to at least one relevant comparator.

5.1 Company cost comparison

5.1.1 Summary of cost comparison

The company presents a cost comparison analysis between BKZ 160 mg every 4 weeks (Q4W) and the following IL-17A inhibitors: IXE 80 mg Q4W, SEC 150 mg per month and SEC 300 mg per month. Separate comparisons are presented for AS and nr-axSpA, but subgroup analyses are not presented. The company justifies the assumption of similar efficacy and safety profile between BKZ and IL-17A inhibitors based on the results of the NMAs presented in Section 3.9. and Appendix D of the CS. The company considers IXE to be the most relevant comparator for both axSpA populations based on i) similarity of treatment effect and ii) an assumption that this is the treatment most likely to be displaced by BKZ (See Section 3.2).

The company's cost-comparison assumes that the only differences in costs between BKZ and comparators, stem from differences in drug acquisition costs of (Section B.4.2.2, CS). All other categories of healthcare resource are assumed equivalent, given the underlying assumption of equivalent efficacy and safety between the treatments under comparison and their common administration method (i.e., SC injection).

The company estimates costs using a cohort model with 4-weekly cycles and a 10-year time horizon. All costs are expressed in 2022/23 prices and undiscounted in the base-case analysis. The EAG considers that all relevant costs have been included in the cost-comparison, with appropriate data sources used to inform these.

Drug acquisition costs are incurred in the model, while individuals remain on treatment. The cohort model tracks the proportion of individuals remaining on treatment over the time horizon conditional on primary response assessment according to BASDAI50 (base-case) at a specific time point for each

drug. Only individuals who achieve primary response ('responders') remain on treatment after response assessment and are exposed to a long-term treatment discontinuation probability from that time point onwards. Individuals who discontinue treatment due to lack of primary response ('non-responders') or long-term treatment discontinuation discontinue, incur no further costs. Response rates and treatment discontinuation probabilities are only conditional on the population (AS and nr-axSpA); no subgroups by prior b/tsDMARD exposure are considered in the cost-comparison analysis. The appropriateness of not performing subgroup analyses is discussed in Section 5.2.1.

Resource use and costs applied in the company's cost comparison are summarised in Table 5. A brief description of the parameterisation and assumptions of the cost comparison are presented in the following sub-sections.

Table 5. Summary of costs in the cost comparison analysis

	BKZ	**IXE**	**SEC 150 mg**	**SEC 300 mg**
Dose schedule	160 mg Q4W	160 mg loading dose, then maintenance 80 mg Q4W	150 mg per week for 5 doses, followed by: 150 mg per month	300 mg per week for 5 doses, Followed by: 300 mg per month
Drug acquisition unit costs	BKZ 160 mg/1 ml solution for injection pre-filled syringes or pens (pack of 2), £2,443 per pack (list price), [redacted] per pack (PAS discount, [redacted])	Taltz 80 mg/1 ml solution for injection pre-filled pens (pack of 1), £1,125 per pack (list price)	Cosentyx 150 mg/1 ml solution for injection pre-filled syringes or pens (pack of 2), £1,218.78 per pack (list price)	Cosentyx 300 mg/2 ml solution for injection pre-filled pens (pack of 1), £1218.78 per pack (list price)
Annual acquisition costs				
. Non-responders (AS & nr-axSpA)	1st year only:[redacted](PAS price)	£1st year only: 6,750 (list price)	1st year only: £4,729 (list price)	1st year only: £9,457 (list price)
. Responders (AS & nr-axSpA) assuming no discontinuation after primary response assessment	1st year: [redacted] (PAS price) Subsequent years: [redacted] (PAS price)	1st year: £15,750 (list price), Subsequent years: £14,625 (list price),	1st year: £9,213 (list price) Subsequent years: £7,288 (list price)	1st year: £18,427 (list price) Subsequent years: £14,575 (list price)

Abbreviations: AS, anklyosing spondylitis; BKZ, bimekizumab; IXE, ixekizumab; nr-axSpA, non-radiographic ankylosing spondyloarthritis; PAS, patient access scheme; Q4W, every 4 weeks; SEC, secukinumab.

5.1.1.1 Acquisition costs

The BKZ drug acquisition unit cost is presented for the drug's list price and with a patient access scheme (PAS), consisting of a simple discount of [redacted] over the list price. The comparators' acquisition unit costs of IXE and SEC only consider their corresponding list prices (see Table 5). List prices for all treatments under comparison were sourced from the BNF 2023.[44-46] The drug acquisition costs and results reported in this document do not reflect the PAS prices of IXE and SEC as these are confidential. The EAG applies PAS prices for all the treatments under comparison in a separate confidential appendix to this report.

The company states the dosing schedules for each treatment were sourced from the corresponding SmPCs, which are summarised in Table 5. The company considers alternative dosing schedules in scenario analysis for SEC 300 mg. Annual acquisition costs are presented separately for treatment responders and non-responders, as time on treatment is dependent on primary response. To simplify presentation of results in Table 5, these were estimated with the long-term treatment discontinuation set to 0%. Annual costs are presented for responders (with and without the long-term treatment discontinuation) and non-responders separately in Table 5. Annual acquisition cost estimates, assume primary response assessment is performed at 16 weeks across all treatments in line with the company's revised base-case assumption (see response to clarification question B1).

5.1.1.2 Response assessment and primary treatment response rates

As mentioned in Section 5.1.1, the company's analysis explicitly models response to biologic treatment, and conditions time on treatment partly on primary treatment response.

In the company's base-case, the primary treatment response date for all treatments is informed by the BASDAI50 score at 16 weeks from the BKZ arm in the BE MOBILE 1 and BE MOBILE 2 trials for nr-axSpA and AS, respectively (see Table 31, CS). The company stated that BE MOBILE 1 and BE-MOBILE 2 efficacy data for BKZ was selected to inform base-case analyses for simplicity, due to i) the underlying assumption of effectiveness equivalence across treatments and ii) *"when all response rates are varied in the same direction and same magnitude for all comparators simultaneously, response rates are not typically a model driver"* (response to clarification question B4). In response to clarification question B4 (Table 16, clarification response) the company conducted sensitivity analyses in which BASDAI50 response was informed by the highest and lowest point estimate BASDAI50 observed for the active treatment (by population nr-axSpA or AS, by prior b/tsDMARD exposure) in a selection of trials used to inform the BASDAI50 NMAs in the current appraisal (see Section 4.2.3.5). The company also presented scenario analyses where response assessment was based on ASAS40 scores for BKZ in the BE MOBILE 1 and BE MOBILE 2 trials.

The population in the BE MOBILE trials include patients with and without prior b/tsDMARD exposure. Thus, the primary response rates applied in the model reflect a mixed population in terms of prior b/tsDMARD exposure, which implicitly assumed that either i) response rates are independent of prior b/tsDMARD exposure or ii) the population in the BE MOBILE trials is reflective of the population in UK clinical practice in terms of proportion of patients with previous b/tsDMARD exposure. The company did not explicitly justify these assumptions.

The time point for primary treatment response assessment was initially assumed by the company to be 16 weeks for BKZ and SEC (150 mg and 300 mg), while for IXE response was assessed at 16-20 weeks. After the clarification stage, the company updated their base-case analysis so that primary response is assessment is assumed to be performed at 16 weeks for all treatments under comparison.

5.1.1.3 Long-term treatment adherence and discontinuation probabilities

The company applied a constant annual discontinuation probability for all treatments under comparison; these probabilities were conditional on population and are reported in Table 32 (CS) alongside the sources informing them. The treatment discontinuation probabilities were informed by previous NICE technology appraisals (TAs).[16, 28, 29, 47] The EAG notes that the annual discontinuation probability in previous NICE TAs in nr-axSpA has not been consistently the same. While the company's estimate (5%) in this population is in line with TA718[16] and Pfizer's submission to TA383,[47] an estimate of 6% has been applied in TA383[47] (EAG preference) and in TA719.[48] The company did not conduct any sensitivity or scenario analyses on these parameters.

5.1.1.4 Time horizon

The time horizon in the company's cost-comparison analysis is assumed to be 10 years, which the company justified as a conservative assumption. Scenario analyses with alternative time horizons (one, two, and five years, and model estimated mean time on treatment [3.10 and 3.97 years for AS and nr-axSpA, respectively]) were also presented by the company.

5.1.1.5 Assumptions

The key assumptions underlying the company's cost comparison analysis are listed below:

- BKZ is positioned as the first-line treatment (after NSAID failure) in patients who are contraindicated to TNF-α inhibitors, and second-line and later for all other patients with axSpA.
- IXE is the most relevant comparator for both AS and nr-axSpA populations (see Section B.3.11 CS).
- Equivalent effectiveness within BKZ and comparators means that it is appropriate to evaluate BKZ in the context of a cost-comparison appraisal.

- Costs associated with drug administration, monitoring and treating adverse events, and disease management are equivalent across the treatments under comparison and are, therefore, excluded from the cost comparison. Cost differences between treatments stem only from differences in drug acquisition costs.
- The time horizon required to capture cost differences between treatments is 10 years.
- Time on treatment is conditional on primary response. Individuals who experience primary treatment response are exposed to a constant long-term treatment discontinuation probability from the point of response assessment onwards.
- Treatment response and long-term treatment discontinuation are conditional on patient population (AS or nr-axSpA), but not patient subgroup (b/tsDMARD-naïve or -experienced).
- Patients who discontinue treatment (due to lack of primary response or over the long-term), are assumed to accrue no further costs.

5.1.2 Results

The company presented mean undiscounted total and incremental costs per patient for each treatment under comparison for the i) nr-axSpA and ii) AS populations.

The company's revised cost comparison analysis results (response to clarification question B1), which include the PAS discount for BKZ and list prices for the comparators, suggest that for both nr-axSpA and AS populations, BKZ is [redacted] compared to IXE and SEC 300 mg. Compared to SEC 150 mg, BKZ may lead [redacted] costs.

The company presents scenario analysis exploring alternative assumptions on i) cost discount rate (Table 37-39, CS), ii) time-point for primary response assessment (Table 37-39, CS), iii) primary response outcome (Table 37-39, CS), iv) preferred evidence sources to inform primary response rates (Table 16, response to clarification question B4), v) SEC 300 mg dosing schedule (Table 37-39, CS; Table 14, response to clarification question B3), and vi) time horizon (Table 37-39, CS; Table 18, response to clarification question B8). The only comparisons in which results appear to be sensitive to alternative assumptions are those against SEC 150 mg, with BKZ becoming [redacted] in the scenario analyses where the following assumptions are applied:

- a low BASDAI50 response rate (31.3% and 21.9% in nr-axSpA and AS, respectively);
- an annual discount rate of 3.5% (AS population only);
- a time horizon equal or lower than 5 years;
- ASAS40 as response outcome (AS population only for which the ASAS40 was 44.8% in the BE-MOBILE 2 trial).

5.2 EAG critique of the company submission

The EAG validated the electronic version of the model by auditing formulae, and verifying model input and output values matched the information provided by the company in the CS, response to clarification questions, and original evidence sources, where applicable. No major errors were identified, and the EAG was satisfied with the internal validity of the electronic version of the model submitted at the clarification stage.

The EAG critique focuses on the following aspects of the cost comparison analysis:

- Population and relevant comparators;
- Primary treatment response;
- Long-term treatment adherence and discontinuation;
- Time horizon.

Following the critique, the EAG proposes an alternative base case analysis, exploring alternative assumptions to those used in the company analysis. The results of the EAG preferred base case and further analyses are presented in a confidential appendix separate to this report.

5.2.1 Population, treatment positioning and relevant comparators

The company positions BKZ at first or subsequent lines of treatment in both the AS and nr-axSpA treatment pathway, but uses the same cost comparison analysis (based on the mixed populations in the BE MOBILE trials) to support its use in b/tsDMARD-naïve and -experienced populations. The company considers IXE to be the relevant comparator for AS and nr-axSpA, regardless of prior exposure to b/tsDMARD. As detailed in Section 3.2, the EAG considers SEC 150 mg to be the relevant comparator for all populations and subgroups in scope for the current appraisal. The EAG's analyses exclude comparisons against SEC 300 mg, as this dosage is not currently recommended by NICE.

The company did not present subgroup analyses by prior b/tsDMARD exposure, as specified in the NICE scope for this appraisal. Since the cost comparison model conditions the proportion of patients on treatment over time on primary treatment response, and response is conditional on prior b/tsDMARD exposure (with lower response rates expected for the b/tsDMARD-experienced subgroup), it is expected that costs will differ across subgroups. This may translate into different cost impacts across treatments in each subgroup, because IXE and SEC require loading (more intensive resource use) in the first cycle in the model compared to BKZ. Thus, the lower the response rate, the more the relative contribution of those loading costs to the total costs will be, which favours treatments without a loading phase (i.e., BKZ). This is revisited in the context of how treatment response (Section 5.2.2) and time horizon affect costs (Section 5.2.4).

Given the i) sparsity of the clinical efficacy evidence for the b/tsDMARD-experienced subgroup particularly for the nr-axSpA (see Sections 3.4 and 4.4), ii) the absence of subgroup cost comparison analyses by prior b/tsDMARD exposure and iii) the likely positioning of BKZ in the treatment pathway (i.e., second and subsequent lines of treatment for the majority of patients), the EAG considers that this is a key area of uncertainty.

5.2.2 Primary treatment response

The company choice of evidence to inform the primary treatment response parameter in the cost comparison analysis, may not be reflective of response rates observed in UK clinical practice with IL-17 inhibitors. First, BASDAI50 probabilities applied in the model for the AS and nr-axSpA population were estimated in mixed populations according to prior b/tsDMARD exposure (only 7.8% and 16.7% of patients in the BKZ arms of BE MOBILE 1 and BE MOBILE 2, respectively) and this distribution may not be reflective of the distribution by prior b/tsDMARD exposure of patients eligible for treatment. Second, clinical advice to the EAG and existing evidence for b/tsDMARD suggests that primary treatment response is lower in patient populations with prior exposure to b/tsDMARDs (Table 16, clarification response to question B4). Therefore, the EAG considers that in principle results of subgroups by prior b/tsDMARD exposure should be more informative to decision makers. However, the EAG recognises that evidence sparsity in the b/tsDMARD-experienced subgroup (particularly in the nr-axSpA population) would hinder interpretation of subgroup results.

Third, the EAG noted in clarification questions (see Question B4) that alternative sources of evidence (including evidence by prior b/tsDMARD exposure), namely using data from SEC (150 mg) and IXE trials, and/or using a pooled response rate for BKZ, SEC 150 mg and IXE estimated through a meta-analysis, could have been used to inform the company's base-case. While the company considers that the response rate would not typically be a model driver (as there are no differences between treatments), the EAG has noted above that the response rate will impact the pattern of resource use over time differently for treatments with loading doses (i.e., SEC and IXE) compared with those without (i.e., BKZ). The company did not provide an analysis where treatment response was informed by pooled evidence for BKZ, SEC 150 mg and IXE, which was one of the approaches suggested by the EAG at the clarification stage. This evidence would have been preferred by the EAG to inform a base-case analysis, as it would have allowed use of all existing evidence and would be in line with the assumption of equivalent efficacy across treatments that underpins the cost comparison analysis. Given the delay in receiving the company's response to clarification questions, the EAG did not have time to update the company's evidence synthesis to generate these estimates. The company did conduct scenario analysis using primary response rates from i) alternative studies and ii) using an alternative response outcome (ASAS40). The results of these analyses for the comparison against

SEC 150 mg, suggest that depending on the source of response data selected SEC 150 mg may be cost saving or cost increasing against BKZ.

Given the evidentiary challenges in obtaining accurate primary response estimates that reflect the efficacy of the treatments under comparison, particularly by to prior b/tsDMARD exposure, the EAGs explores the impact of both uncertainty and heterogeneity affecting primary response estimates by replicating the company's analyses at lowest and highest observed BASDAI50 probabilities and with confidential PAS prices for all treatments under comparison (in the confidential appendix separate to this report).

5.2.3 Long-term treatment adherence and discontinuation

The EAG considers there is substantial uncertainty regarding the long-term treatment discontinuation probability for BKZ in clinical practice. While the company's safety and discontinuation outcomes NMAs (see Section 4.2) suggest no evidence of difference in discontinuation compared to SEC 150 mg and IXE, no evidence has been presented for the assumption of equivalence in long-term maintenance of the treatment effect (leading to continued treatment adherence). The EAG notes that a cost comparison analysis requires reasonable certainty of equivalence between treatments in long-term treatment effectiveness. If there are differences in long-term discontinuation between treatments, the cost comparison framework is unable to capture the consequences of any scenario in which loss of efficacy, or AEs leads to differential discontinuation rates.

Even if there are no differences in long-term treatment discontinuation probabilities between treatments, there is still uncertainty on whether the discontinuation probabilities applied in the model are reflective of treatment adherence in UK clinical practice. This is because the evidence used to inform these parameters in previous TAs and in the current submission was generated in the context of TA383[47] and is, therefore, outdated. The EAG requested at clarification stage for the company to comment on whether there is more contemporaneous evidence on probabilities of long-term treatment discontinuation (conditional on achieving primary treatment response) and to present sensitivity analyses using these alternative estimates. While the company presented short summaries of studies that could potentially inform sensitivity analyses on these parameters (response to clarification question B6), they did not conduct any such analyses and do not report any alternative estimates that could be used for this purpose.

Since long-term discontinuation probabilities are used (alongside primary treatment response probabilities) to determine the proportion of patients on treatment over time in the cost-comparison model, these parameters partly determine mean time on treatment (i.e., the relevant time horizon, see Section 5.2.4). The EAG explores uncertainty in long-term discontinuation in the analyses presented in the confidential appendix to this report.

The EAG notes that the impact of uncertainty on treatment discontinuation (due to lack of primary response or loss of treatment effect or tolerability) can only be fully accounted by modelling treatment sequencing in the context of a cost-utility framework. Thus, this uncertainty cannot be explored in the cost-comparison evaluation process.

5.2.4 Time horizon

The EAG agrees that under the company's base-case assumptions and applying the list prices available for the comparators in their analyses, a 10-year time horizon is likely to be conservative towards BKZ (company's response to clarification question B8). This is because a higher number of doses is costed in the first model cycle for IXE (3 doses) and SEC (5 doses) compared to BKZ (2 doses). For subsequent model cycles, BKZ and IXE incur the cost of one dose per 4-weekly cycle while SEC incurs the cost of 0.92 doses (equivalent to one dose per month). This means that due to higher initial costs of loading SEC 150 mg compared to BKZ, longer time horizons will favour this drug when compared to BKZ.

Clinical advice to the EAG suggested that mean time on treatment is two to three years for IXE and 18 months to three years for SEC. The clinical advisors agreed that at second and further lines of treatment, mean treatment duration is likely to be shorter. The company provided in their response to clarification question B8, an analysis assuming that mean time on treatment is 3.1 and 3.97 years for AS and nr-axSpA, respectively. Although this is not explicit in the documentation submitted by the company at the clarification stage, the mean time on treatment estimates correspond to the area under the curve for the proportion of patients on-treatment over the 10-year time horizon as predicted by the economic model. Since at the end of the time horizon the model predicts that a proportion of patients still remain on treatment (15% and 29% for AS and nr-axSpA, respectively), the estimated mean treatment duration is actually a restricted mean due to censorship at 10 years. Therefore, the EAG does not consider this estimated mean treatment duration to be meaningful.

In the context of a cost-comparison accrued costs need to be estimated over a time horizon appropriately representing a typical course of treatment. Thus, the most relevant time horizon should reflect the mean duration of treatment in clinical practice. As this is uncertain, the EAG analyses consider a range of time horizons up to ten years.

5.3 Summary of EAG's view

- The EAG considers that the company's cost comparison model is in line with previous NICE TAs[16, 47, 48] and appropriate to inform decision making, and that all relevant costs have been included in the cost-comparison analyses.

- The company's analyses, which do not include confidential commercial arrangements for the comparators, suggest that BKZ is [redacted] compared to the most relevant comparator, SEC 150 mg, and [redacted] compared to IXE.
- The EAG considers that the relevant time horizon is uncertain, as are the primary treatment response rates and the long-term discontinuation probabilities.
- Given that primary treatment response is likely to be conditional on prior b/tsDMARD exposure (treatment efficacy expected to be lower in the b/tsDMARD-experienced subgroup) and that BKZ is likely to be positioned at second and subsequent lines of treatment, subgroup analyses should have been performed. The EAG recognises, however, the evidentiary challenges in appropriately parameterising subgroup analyses for the b/tsDMARD-experienced subgroup.

6 COMPANY AND EAG COST COMPARISON RESULTS

The company's base-case and its assumptions have been described in Section 5.1.1. The EAG base-case applies the same set of assumptions as in the company's analyses, but results are presented at a range of time horizon values recognising that the relevant time horizon is uncertain. When alternative time horizons are considered, the company's 10-year time horizon assumption is shown to be conservative in the company's and EAG's analyses.

7 EQUALITIES AND INNOVATION

The company submission notes that nr-axSpA is more prevalent in females than males and females typically have a worse response to TNF-α inhibitors than males. Clinical advisors to the EAG agreed that nr-axSpA is more prevalent in females. The clinical advisors also noted that while the response to TNF-α inhibitors is lower in females, the reasons for this are more complicated than just biological differences between males and females. Potential factors for the poorer response in females include how nr-axSpA is diagnosed and which outcomes are used to measure response. However, the company does not provide any argument on how BKZ may help to address these health inequalities. Previous appraisals including of comparator treatments IXE and SEC (TA407,[28] TA718[16] and TA719[30]) noted no equality issues.

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

8.1 Strengths

8.1.1 Clinical evidence

- The clinical trial evidence submitted has sufficiently robust internal validity and its applicability to the NHS was acceptable.
- The evidence provided to compare BKZ to SEC and IXE in b/tsDMARD-naïve and -experienced populations at the time of response assessment is limited but supports the assumption of equivalent efficacy and safety against these comparators.

8.1.2 Economic evidence

- The electronic model used to inform the cost comparison analysis is simple and transparently presented, with no major errors identified.
- The cost comparison analysis explicitly models primary treatment response and long-term discontinuation, which is in line with the assumptions of cost-utility models in previous NICE TAs in axSpA.[16, 28, 47, 48]
- All relevant cost categories have been included in the company's cost comparison analysis, and the evidence sources used to inform costs were appropriate.

8.2 Weaknesses and areas of uncertainty

8.2.1 Clinical evidence

- The company's preferred comparator IXE has a smaller market share than SEC in the b/tsDMARD-experienced axSpA population and in the b/tsDMARD-naïve when TNF-α inhibitors are contraindicated. The company's arguments for selecting IXE over SEC as the comparator of interest were not convincing. The EAG prefer SEC 150 mg as the comparator of interest.
- Networks of evidence are sparse meaning that relative effect estimates comparing BKZ to SEC and IXE are uncertain, particularly for the b/tsDMARD-experienced population. There is no comparative evidence for b/tsDMARD-experienced patients with nr-axSpA.
- Evidence suggests heterogeneity in primary treatment response according to prior b/tsDMARD exposure, with treatment efficacy expected to be lower in the b/tsDMARD-experienced subgroup. However, clinical evidence to inform the b/tsDMARD-experienced subgroup is scarce. This may be of particular importance for BKZ as it is likely to be

positioned at second- and subsequent lines of treatment for the majority of patients in UK clinical practice.

- Due to evidence sparseness potential sources of heterogeneity in the evidence could not be adequately explored.
- The assumption of equivalent efficacy and safety (adherence and discontinuation) between BKZ and the comparators beyond the initial response assessment is uncertain.

8.2.2 Economic evidence

- The appropriateness of assessing the cost-effectiveness of BKZ in the context of a cost comparison relies on the validity of the assumption of equivalent efficacy and safety of BKZ to at least one relevant comparator.
- The most relevant time horizon for the cost comparison analysis is uncertain. While the magnitude of cost differences cost differences between BKZ and comparators for the EAG and company's base case results is sensitive to this parameter when confidential PAS prices are considered for all treatments, the interpretation of the results as cost saving or cost increasing does not change over a time horizon value range from 1 to 10 years.
- Other areas of uncertainty include the primary treatment response rates and the long-term discontinuation probabilities, which determine time on treatment in the cost-comparison model. While the EAG sensitivity analyses found the results robust to alternative assumptions on these parameters, the impact of treatment discontinuation (due to lack of primary response or loss of treatment effect or tolerability) can only be fully accounted for by modelling treatment sequencing in the context of a cost-utility framework.

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APPENDIX 1 TABLES WITH PREFERRED MODELS AND RESULTS OF THE NMAS

Table 6. Models explored in previous appraisals.

Indication	Appraisal	Drug		Models Explored	
			Time-points Assessed	Fixed/Random-Effects	Placebo-Adjusted
AS and nr-axSpA	TA383	TNF-α inhibitors	Weeks 10-16	FE and RE; FE preferred	Yes
	TA718	Ixekizumab	Weeks 12-16	FE only	No
	ID6245, this Appraisal	**Bimekizumab**	**Weeks 12-16***	**FE and RE; (Details on preferred models in Table 7)**	**Yes**
AS	TA407	Secukinumab	Weeks 12-16	FE and RE, FE preferred	Yes
	TA829	Updacitinib	Weeks 12-16	FE and RE; FE preferred	Yes
nr-axSpA	TA497	Golimumab	Weeks 12-16	FE only	No
	TA719	Secukinumab	Weeks 12-16	FE only	Yes
	TA861	Updacitinib	Weeks 14-16†	FE and RE; FE preferred	Yes

* If studies reported measurements at more than one time-point, 16-week data were preferred. † Used for primary analysis, secondary analyses using week 12-16 data were also conducted.
Abbreviations: AS, ankylosing spondylitis, FE, fixed-effect; nr-axSpA, non-radiographic axial spondyloarthritis, RE, random-effects; TNF, tumour necrosis factor

Table 7. Results for NMAs using the company's preferred models

Indication	Population	Outcome-Type	Outcome	Company's preferred model	Relative effects	
					IXE vs. BKZ	SEC vs. BKZ
nr-axSpA	Predominantly b/tsDMARD-naive	Dichotomous OR (95% CrI)	ASAS20	Fixed-effect	1.97 (0.89, 4.35)	**2.29 (1.19, 4.53)**
			ASAS40	Fixed-effect	1.46 (0.58, 3.52)	1.97 (0.95, 4.13)
			BASDAI50	Fixed-effect	1.17 (0.47, 2.97)	1.46 (0.73, 3.11)
		Continuous MD (95% CrI)	BASDAI CFB	Fixed-effect	**-0.91 (-1.69, -0.09)**	-0.68 (-1.48, 0.12)
			BASFI CFB	Fixed-effect	**-0.86 (-1.71, -0.08)**	**-0.79 (-1.58, -0.04)**
AS	Predominantly b/tsDMARD-naive	Dichotomous OR (95% CrI)	ASAS20	Placebo adjusted random-effects*	1.02 (0.53, 2.01)	1.26 (0.71, 2.11)
			ASAS40	Placebo adjusted fixed-effect	0.99 (0.62, 1.50)	1.13 (0.85, 1.53)
			BASDAI50	Placebo adjusted fixed-effect	0.88 (0.46, 1.59)	1.53 (0.89, 2.49)
		Continuous MD (95% CrI)	BASDAI CFB	Placebo adjusted fixed-effect	0.19 (-0.29, 0.76)	-0.20 (-0.58, 0.16)
			BASFI CFB	Placebo adjusted fixed-effect	-0.09 (-0.57, 0.39)	0.46 (-0.16, 1.12)
	b/tsDMARD-experienced	Dichotomous OR (95% CrI)	ASAS20	Placebo adjusted fixed-effect*	1.50 (0.35, 4.75)	1.13 (0.36, 3.93)
			ASAS40	Placebo adjusted fixed-effect	1.94 (0.83, 4.43)	0.86 (0.39, 1.87)
			BASDAI50	Fixed effect	0.38 (0.09, 1.68)	--
		Continuous MD (95% CrI)	BASDAI CFB	Placebo adjusted fixed-effect*	0.84 (-3.85, 4.47)	0.53 (-2.77, 3.22)
			BASFI CFB	Fixed-effect	-0.26 (-1.36, 0.91)	--
nr-axSpA and AS combined	Mixed	Safety and tolerability OR (95% CrI)	Discontinuation due to any reason	Fixed-effect	0.97 (0.33, 2.91)	1.04 (0.36, 3.05)
			Discontinuation due to AEs	Fixed-effect	0.65 (0.14, 3.13)	0.66 (0.14, 3.18)
			SAEs	Fixed-effect	1.18 (0.23, 6.67)	0.76 (0.16, 3.79)

Results in bold text suggest there may be a difference in treatment effect. * The EAG preferred a different model using the model fit details provided in Appendix D.

Abbreviations: AE, adverse events; AS, ankylosing spondylitis; BKZ, bimekizumab; b/tsDMARD, biologic/targeted synthetic disease modifying anti-rheumatic drug; CFB, change from baseline; CrI, credible interval; IXE, ixekizumab; MD, mean difference; nr-axSpA, non-radiographic axial spondyloarthritis; OR, odds ratio; SAE, severe adverse events; SEC, secukinumab

Table 8. Studies of bimekizumab, secukinumab and ixekizumab included in the NMAs for the outcomes of interest

Indication	Outcome	predominantly b/tsDMARD-naive			b/tsDMARD-experienced		
		Bimekizumab	Ixekizumab	Secukinumab	Bimekizumab	Ixekizumab	Secukinumab
AS	ASAS20	BE AGILE[49] BE MOBILE 2[42]	COAST-V[22]	ASTRUM[50] MEASURE 2[51] MEASURE 4[26] MEASURE 5[52]	BE MOBILE 2[42†]	COAST-W[23]	ASTRUM[50†] MEASURE 2[51†] MEASURE 4[26†] MEASURE 5[52†]
	ASAS40	BE AGILE[49] BE MOBILE 2[42]	COAST-V[22]	ASTRUM[50] MEASURE 2[51] MEASURE 4[26] MEASURE 5[52]	BE MOBILE 2[42†]	COAST-W[23]	ASTRUM[50†] MEASURE 2[51†] MEASURE 4[26†] MEASURE 5[52†]
	BASDAI50	BE AGILE[49] BE MOBILE 2[42]	COAST-V[22]	ASTRUM[50] MEASURE 2[51]	BE MOBILE 2[42†]	COAST-W[23]	---
	BASDAI CFB	BE AGILE[49] BE MOBILE 2[53]	COAST-V[22]	ASTRUM[50] MEASURE 2[51] MEASURE 4[26] MEASURE 5[52]	BE MOBILE 2[42†]	COAST-W[23]	MEASURE 2[51†] MEASURE 4[26†] MEASURE 5[52†]
	BASFI CFB	BE AGILE[49] BE MOBILE 2[42]	COAST-V[22]	MEASURE 2[51]	BE MOBILE 2[42†]	COAST-W[23]	---
nr-axSpA	ASAS20	BE MOBILE 1[41]	COAST-X[21]	---			
	ASAS40	BE MOBILE 1[41]	COAST-X[21]	PREVENT[54]			
	BASDAI50	BE MOBILE 1[41]	COAST-X[21]	PREVENT[54]			
	BASDAI CFB	BE MOBILE 1[41]	COAST-X[21]	---			
	BASFI CFB	BE MOBILE 1[41]	COAST-X[21]	---			

[†]Data were from the b/tsDMARD-experienced subgroup

Abbreviations: AS, ankylosing spondylitis, b/tsDMARD, biologic/targeted synthetic disease modifying anti-rheumatic drug; CFB, change from baseline; nr-axSpA, non-radiographic axial spondyloarthritis, NMA, network meta-analysis.

Table 9. Discontinuation rates at 16 weeks in clinical trials of BKZ, SEC and IXE.

Clinical trial	Intervention	Population	Discontinuation measure at 16 weeks	Proportion discontinuing
BE MOBILE 1	BKZ 160 mg	nr-axSpA Mixed but predominantly b/tsDMARD-naïve	TEAEs leading to discontinuation of trial drug	1.6%
BE MOBILE 2	BKZ 160 mg	AS Mixed but predominantly b/tsDMARD-naïve	TEAEs leading to discontinuation of trial drug	2.7%
COAST-X[21]	IXE 80 mg	nr-axSpA b/tsDMARD-naïve	Discontinuation due to AE	IXEQ2W 1% IXEQ4W 1%
COAST-V[22]	IXE 80 mg	AS b/tsDMARD-naïve	Discontinuation due to any AE	IXEQ2W 4% IXEQ4W 0%
COAST-W[23]	IXE 80 mg	AS b/tsDMARD-experienced.	Discontinuation due to AE	IXEQ2W 3.1% IXEQ4W 8.8%
MEASURE 4[26]	SEC 150 mg	AS Mixed but predominantly b/tsDAMRD-naïve	Discontinued due to any AEs	Load dose 0.9% No load – 1.7%

Abbreviations: AE, adverse event, AS, ankylosing spondylitis; BKZ, bimekizumab, b/tsDMARD, biologic/targeted synthetic disease-modifying anti-rhematic drug; IXE, ixekizumab, nr-axSpA, non-radiographic axial spondyloarthritis; Q2W, every 2 weeks; Q4W, every 4 weeks; SEC, secukinumab; TEAE, treatment-emergent adverse events.

Single Technology Appraisal

Bimekizumab for treating axial spondyloarthritis [ID6245]

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 **27 July 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the chair and vice chair 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 Choice of comparator

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 2, Section 1.1	Please amend the following statement: "This contrasts with the company's proposed comparator, ixekizumab (IXE), which the EAG believe is less used than SEC 150 mg at this line of therapy" To "This contrasts with the company's proposed most relevant comparator, ixekizumab (IXE) (among IXE, SEC 150 mg, and SEC 300 mg), which the EAG believe is less used than SEC 150 mg at this line of therapy"	This is not an accurate depiction of UCB's position. After discussion in the NICE decision problem meeting, UCB proposed a most relevant comparator, IXE. UCB included SEC 150 mg and SEC 300 mg as relevant comparators, in line with the decision problem defined in the final scope issued by NICE (1). Published NICE guidance provides no direction on market share thresholds for comparators allowed in a technology appraisal (2). In TA803, an FTA, risankizumab was compared with guselkumab, which had minimal market share, based on clinical similarity (3).	The sentence was amended to: "This contrasts with the company's proposed most relevant comparator, ixekizumab (IXE), which the EAG believe is less used than SEC 150 mg at this line of therapy"

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 10, paragraph 1	Please amend the following text: "The company claim that IXE is most likely to be displaced by BKZ and use this as justification for choosing IXE as the main comparator in this appraisal" To: "The company claim that IXE is most likely to be displaced by BKZ and use this as justification for choosing IXE as the most relevant comparator in this appraisal"	This is a factually inaccurate depiction of UCB's presentation of comparators and of published NICE guidance on inclusion of comparators. NICE guidance does not specify a "main" comparator it provides rules for determining if comparator(s) are relevant (2). In response to discussions at the NICE decision problem meeting UCB included justification for the 'most relevant' comparator being IXE. UCB did not say that other comparators were not relevant.	This has been changed to: "The company claim that IXE is most likely to be displaced by BKZ and use this as justification for choosing IXE as the ~~main~~ most relevant comparator in this appraisal"
Page 10, paragraph 1	Please add an additional statement to the end of the following text to provide sufficient context:	This contains factual omissions that affect interpretation. UCB provided additional justification during	This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	"The company claim that IXE is most likely to be displaced by BKZ and use this as justification for choosing IXE as the comparator in this appraisal. Additional justifications provided by the company include advice from nine UK clinicians who consider BKZ and IXE to be similar in terms of efficacy and safety, IXE having the most similar efficacy in NMAs, IXE having the most similar pathway position for both b/tsDMARD-naïve and b/tsDMARD experienced patients, IXE being the most similarly administered treatment, and UK market research and independent international real-world data suggesting a trend towards increasing use of SEC 300 mg in the UK and internationally (4-7).	clarification questions and in the submission.	It is not the role of the EAR to repeat all the company's arguments. A reference to the section in the submission that makes these points has been added "(CS, Section B.1.1.1)".
Page 10, paragraph 1	Please amend the following text: The company have also included evidence for comparison to SEC 150 mg, but it was not considered the main comparator To:	This presents a factually inaccurate representation of what the company presented and implies requirements that are not in NICE guidance. NICE guidance does not specify	This has been changed to: "The company have also included evidence for comparison to SEC 150 mg and SEC 300 mg, but ~~it was~~ they were not considered the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	"The company have also included evidence for comparison to SEC 150 mg and SEC 300 mg, but they were not considered the most relevant comparator"	a "main" comparator (2). In response to discussions at the NICE decision problem meeting, UCB defined the 'most relevant' comparator, but included three relevant comparators.	~~main~~ most relevant comparator"
Page 10, paragraph 4	Please add an additional statement to the end of the following text to provide sufficient context: "However, the EAG's clinical advisers noted that Figure 1 in the CS describing the treatment pathway, should also include SEC as a first line biologic option for patients with nr-axSpA. This supports the company conclusion that SEC 300 mg is used in 2nd line across axSpA. Market research data provided by the company estimate that SEC has a 14% market share in b/tsDMARD-naïve patients."	Missing context to the market share interpretation.	No change. This is not a factual inaccuracy. Suggested text does not relate to the pathway which is what is being described in this paragraph.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12, paragraph 1	Please add an additional statement to the end of the following text to provide sufficient context: "Patients presenting with psoriasis (affecting ~10% of axSpA patients[4]), would be more likely to receive an IL-17 inhibitor earlier in the treatment pathway, as there is evidence that this class of biologics are effective at treating this symptom. As noted by the company, patients with concomitant psoriasis would be more likely to receive a 300mg dose of SEC because the SEC 150mg dose is not licensed in plaque psoriasis. Similarly, b/tsDMARD experienced patients, patients with concomitant PsA, and heavier patients (greater than 90kg) would be more likely to receive a 300 mg dose of SEC than patients without these patient characteristics. This is consistent with SEC's SmPC (8).	EAG presentation does not allow correct interpretation of facts surrounding SEC licence. Additional context of the disease area and treatment needed.	No change. This is not a factual inaccuracy.
Page 12, Section 3.2	Please amend the following text to more accurately reflect the various	UCB provided contrasting data sources for market share that refute this	This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	market share data sources provided by UCB during the submission process: "SEC 150 mg is usually preferred with the 300 mg dose being rarely used for axSpA" To: "SEC 150 mg is usually preferred, with a growing trend towards the 300 mg dose"	statement, and should be included for completeness and transparency. In line with the response to clarification questions: Market research commissioned by UCB with 50 independent rheumatologists (43 based in England, 3 in Scotland, and 4 in Wales) treating 6,183 adult axSpA patients in the last 12 months showed that, in patients receiving secukinumab, the 300 mg dose is used in 25% of patients with nr-axSpA (off label dose) and 34% of patients with AS (9). Overall, this market research shows that approximately 30% of secukinumab use in axSpA is at the 300mg dose. This is consistent with an additional independent	This is describing independent clinical advice to the EAG.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		market research source reporting that in the UK between 2021 and 2022, 29.2% of patients who received secukinumab received the 300 mg dose (10).	
Page 12, Section 3.2	Please add an additional statement to the end of the following text to provide sufficient context: "This is justified by claims that IXE is the most similar treatment to BKZ in terms of efficacy and safety and that the evidence for SEC is more heterogeneous with both 150 mg and 300 mg doses being in use and trials reporting results for SEC administered by intravenous (IV) induction rather than the SC administration of SEC in clinical practice. Further support provided by the company include advice from nine UK clinicians who consider BKZ and IXE to be similar in terms of efficacy and safety, IXE being the most similarly administered treatment and having the most similar	Additional justification included during clarification questions and submission omitted.	This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	clinical trial structures, two independent UK market research reports indicating that approximately 30% of secukinumab use in axSpA is composed of SEC 300 mg (9), and additional international real-world evidence suggesting a consistent trend towards increasing use of SEC 300 mg in the (4-7).		
Page 13, paragraph 2	Please add an additional statement to the end of the following text to provide sufficient context: "This is based on clinical experience of SEC being more efficacious than IXE, and adverse injection site reactions associated with IXE, which can cause patients to have poor adherence and/or discontinue this medication. However, 9 UK rheumatologists consulted in the company's advisory boards considered SEC and IXE to be similar in terms of efficacy and safety. The NMA in the company submission also supports a conclusion of similar efficacy between IXE and SEC. Furthermore, as noted in the	Additional context is needed because clinical opinion can vary. UCB submitted new information on injection site reactions to IXE during clarification which counters the clinical opinion presented by the EAG.	This is not a factual inaccuracy. The EAG is accurately describing the independent clinical advice that was received.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	clarification questions response, IXE injection site reactions should be expected to decrease based on the EMA approval of a citrate free formulation in December 2021 (11).”		
Page 13, paragraph 4	Please amend to include red text: [redacted] The company budget impact model splits the total market share of SEC into SEC150 mg, and SEC300 mg doses by axSpA sub-population (nr-axSpA and AS) using estimates from market research (9). The SEC150 mg market shares are 21.3% in nr-axSpA and 18.7% in AS.	The data presented do not reflect that secukinumab market share is split into two doses. In the budget impact model UCB weighted the doses based on independent market research which gave different proportions for of use of SEC 300 mg for each of nr-axSpA and AS. Please also see marking revisions for the marked text.	This is not a factual inaccuracy. The EAG are summarising what is reported in the market share analysis excel file ‘RxY. Data on file. CONFIDENTIAL. AxSpA market share analysis. 2022 AD’. The EAG have noted on pg. 14 that estimates for the split between doses was informed by the patient chart review and Cosentyx Therapy Watch, the methodology of which the EAG has not been able to validate. As such, the suggested changes have not been made to the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	SEC 300 mg market shares were 7.1% in nr-axSpA and 9.6% in AS.		However, the following sentence in the paragraph after Table 2 has been amended for clarity: 'the company has provided estimates for the proportion of patients receiving SEC 300 mg in clinical practice, The ERG notes these estimates are based on market research conducted in the UK..."
Page 14, Table 2	Please amend the presentation of Table 2 to reflect that SEC market share is split in switch population by SEC 150 and SEC 300 shares: SEC 150 share = 19.9%. SEC 300 share = 8.5%. IXE share = 17.9%. IXE + SEC 300 share = 26.4%.	The current format of Table 2 is misleading as SEC 300 has incorrectly been omitted. Note that market shares for SEC 150 (21.3% in nr-axSpA and 18.7% in AS) and SEC 300 (7.1% in nr-axSpA and 9.6% in AS) have been weighted in line with market research data distribution of patients between AS, nr-axSpA and	Table 2 accurately summarises data provided in the market share analysis excel file 'RxY. Data on file. CONFIDENTIAL. AxSpA market share analysis. 2022 AD'. The table does not omit SEC 300 mg, because the company did not distinguish between doses within this document. As these weighted market share estimates were not provided by the company

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		undefined radiographic status (9).	previously, no amendments have been made to Table 2, as new information should not be considered at the FAC stage.
Page 14, paragraph 2	Please amend: "the company's estimate for the proportion of patients receiving SEC 300 mg in clinical practice is based in part on observational data[8-10] (received as part of the company's clarification response to question A1) from other jurisdictions, which is unlikely to be relevant to the UK, as well as a chart review[11] and the Cosentyx Therapy watch" To: "the company's estimate for the proportion of patients receiving SEC 300 mg in clinical practice is based on a UK market research with 50 independent rheumatologists (9) validated by another source of UK market research (10), and supported by real world data from Spain, Germany and the USA[8-10] (received as	The current statement inaccurately suggests that the primary source of market data is observational data from other countries, when this was used to support the UK specific sources provided. Both UK sources support roughly 30% of secukinumab use across axSpA being the 300 mg dose, regardless of radiographic status. The non-UK data was presented to reinforce that increasing SEC 300 mg use is an international trend.	This sentence does not imply the observational evidence is the primary source. To clarify this has been amended to: "the company has provided estimates for the proportion of patients receiving SEC 300 mg in clinical practice. The EAG notes that these estimates are based on market research conducted in the UK,[8,9] but the methodology used in one of these references was not provided by the company,[9] and therefore, could not be validated by the EAG. The company also presented observational data[10-12] (company's response to clarification question A1) as

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	part of the company's clarification response to question A1)."		supporting evidence for the use of SEC 300 mg. Given that these studies refer to the use of SEC in other jurisdictions, the EAG consider these unlikely to be relevant to the UK."
Page 14, bullet 2	Please amend: "the company's own budget impact analysis suggests a higher proportion of patients treated with SEC 150 mg compared to IXE" To: "the company's own budget impact analysis suggests a similar proportion of patients treated with SEC 150 mg (21.3% in nr-axSpA and 18.7% in AS) compared to IXE (17.9%)"	The current statement is inaccurate and misleading as per the previous correction to market share interpretation, SEC 150 mg (21.3% in nr-axSpA and 18.7% in AS) and IXE (17.9) (9) have similar market shares.	As these figures are higher than 17.9%, this is not a factual inaccuracy. However, confidential marking has been removed (as it has been unmarked by the company in this response). The EAG also note that in the company's budget impact analysis document Tables 10 and 12 (world without BKZ, first year), market share estimates for nr-axSpA and AS for SEC 150mg are [redacted] and [redacted] respectively whilst estimates for IXI are [redacted] in both populations, indicating a

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			higher proportion of patients treated with SEC 150 mg compared to IXE. As such, the text has not been amended.
Page 14, bullet 3	Please add a statement to the following text to add sufficient context: The company's own advisory boards estimated that [redacted]. However, as the variation between clinicians was high, the company commissioned additional UK market research to supplement syndicated UK market research data from Therapy Watch. This commissioned work estimated that SEC 300 mg use in AS was 34% and SEC 300 use in nr-axSpA and unidentified axSpA was 25%. When pooled, the estimated use of SEC 300 mg is 30%. This is in concordance with the independently collected data from Therapy Watch	This is not an accurate depiction of the totality of evidence provided by UCB. Additional context added to demonstrate that clinician advice was varied, but supported by two pieces of UK specific market research.	Not a factual inaccuracy. The EAG is summarising the evidence presented.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	that estimated SEC 300 use across axSpA at 29.2%.		
Page 15, paragraph 1	Please amend the statement: "the company's own data [redacted]" to: "the data submitted by the company from RxY syndicated market research with an assumption of the uptake of the two SEC doses from market research (25% SEC300 mg usage in nr-axSpA and 34% SEC300 mg usage in AS, respectively) showed similar market share between SEC 150 mg (21.3% in nr-axSpA and 18.7% in AS) and IXE (17.9%) (9)	Correction to interpretation of market share data. Furthermore, this statement suggests that the data was produced by UCB, when it was instead produced by external market research.	Amended to "data provided by the company in their budget impact analysis showed [redacted]"
Page 15, paragraph 1	Please remove: "as the decision of which comparator is most appropriate should be made according to which treatment has the highest market share in a given positioning in the pathway, not which treatment is most easy to displace"	This is a factually inaccurate representation of NICE methods. NICE guidance language relates to the inclusion of relevant comparators. The criteria for determining whether	Deleted.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		comparators are relevant are given in Section 6.2.1 – 6.2.4 in NICE health technology evaluations: the manual (2). Market share is not mentioned in NICE methods guidance as reason for or against inclusion of a comparator. NICE guidance does not stipulate that any single comparator need be determined most appropriate.	
Page 16, bullet 2	Please remove the following text: "The IL- 17 inhibitor SEC 150 mg is a more appropriate comparator as it has a greater market share in the proposed positioning for axSpA"	As per previous correction to market share interpretation, SEC 150 mg (21.3% in nr-axSpA and 18.7% in AS) and IXE (17.9) have similar market shares, and should be assessed alongside SEC 300 mg, which is commonly used in NHS clinical practice based on two independent pieces of	Amended to "The IL- 17 inhibitor SEC 150 mg is a more appropriate comparator as clinical advice to the EAG is that it is most commonly used ~~it has a greater market share~~ in the proposed positioning for axSpA"

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		market research representing more than 50 rheumatologists in the NHS.	
Cost-comparison consideration omits all analyses pertaining to SEC 300 mg, which is a relevant comparator (Section 5 and Section 6)	Please remove statements pertaining to: “The EAG’s analyses exclude comparisons against SEC 300 mg, as this dosage is not currently recommended by NICE.” and then please include SEC 300 mg as a comparator in all assessments and analyses.	Given the circumstances of SEC 300 mg becoming licenced in the UK, it should not need to be recommended by NICE to be considered an appropriate comparator. The licence extension of SEC 300mg is not eligible to be appraised under NICE’s remit under the 2019 VPAS, or under 2022 topic selection guidance (see PMG47, Section 4.1.4). This is because this extension is not for a first indication or adding a significant new therapeutic indication. NICE concluded that an update was not necessary	Not a factual inaccuracy. The EAG does not consider SEC 300 mg to be relevant.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		to TA407 in October 2020. The licence extension for SEC 300 mg in AS was approved in 2019. The only way for SEC 300 mg to be included in NICE guidance would be through an update of NG65 Spondyloarthritis in over 16s: diagnosis and management, which has not been updated since 2017. It would be inappropriate for NICE to remove a comparator that meets all requirements laid out in Sections 6.2.1 to 6.2.4 in the NICE Methods guide because of a hole in NICE's remit that is accentuated by Section 4.2.13's inconsistency with other rules for comparators (2).	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		As SEC 300 mg is used in UK clinical practice, it should be included in the analyses in order to allow the committee to assess whether it is in line with NICE criteria for a relevant comparator.	

Issue 2 Clarity

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 9, paragraph 1	The absolute rate of adverse events is an inadequate measure of incidence, as it does not adjust for exposure changes over time. Please amend the statement below to reflect conclusions based on EAIR: "With the long-term use (up to week 156) there was an increase in the treatment emergent adverse events (TEAEs) reported"	The text will cause inaccurate conclusions based on incomplete data. While it is true that adverse event rates increase over time in the trial, it is also true that exposure to drug increases. The more relevant measure of adverse events rates is exposure-adjusted incidence rate (EAIR). For BE MOBILE 1, BE MOBILE 2 and BE AGILE 1 & 2, EAIR decreases with time for the any TEAE category of adverse events. The correct interpretation of these data is that no new safety signals were observed with increasing length of follow-up (12-14). This is in line with the conclusion of the BE AGILE 3yr publication: The safety profile of bimekizumab was found to be consistent with previously demonstrated findings, and no new safety signals were identified (15).	Not a factual inaccuracy, events do increase as the company admits.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 9, paragraph 2	Please amend: “Furthermore, there is uncertainty on whether the discontinuation probabilities applied in the model are reflective of treatment adherence in UK clinical practice, as evidence sources for these parameters are outdated and the company did not identify alternative values from more appropriate data sources” To: “Furthermore, there is uncertainty on whether the discontinuation probabilities applied in the model are reflective of treatment adherence in UK clinical practice, as evidence sources for these parameters are outdated and the company did not identify alternative values from more appropriate data sources. However, the company did provide additional supporting evidence for the discontinuation probabilities applied in the model, including providing summaries of RWE discontinuation for secukinumab and TNF-α inhibitors with studies published as recently as 2022. These up-to-date studies provided no evidence that	The current description does not present a factually accurate representation of what the company supplied in response to clarification.	Not a factual inaccuracy. In section 5.2.2 we note this additional information provided by the company. However, the issue is not whether IL-17s have similar discontinuation rates to TNF alpha inhibitors, but whether discontinuation rates in the NICE TA383 are still reflective of long-term discontinuation in current clinical practice.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	secukinumab discontinuation was different than TNF-α discontinuation. There was no RWE for ixekizumab discontinuation identified. In the absence of evidence that there are different discontinuation rates within IL17 inhibitors, UCB chose to use discontinuation rates that are aligned with the majority of previous appraisals in axSpA."		
Page 9, Section 2	Please amend the following text: "The company are claiming similarity or superiority in efficacy and similarity in safety compared to IXE which is the company's chosen comparator treatment, claiming that BKZ has greater or equivalent affinity for IL-17A than IXE in vitro." To: "The company are claiming similarity or superiority in efficacy and similarity in safety compared to IXE, which was considered the most relevant treatment by the company, claiming that BKZ and IXE have equivalent affinity for binding	Inaccurate representation of the position taken by the company.	Amended to "The company are claiming similarity or superiority in efficacy and similarity in safety compared to IXE, which was considered the most relevant treatment by the company, claiming that BKZ and IXE have ~~has greater or~~ equivalent affinity for binding to IL-17A ~~than IXE~~ in vitro."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	to IL-17A, while secukinumab has a lower affinity (16, 17), in vitro.”		
Page 10, second paragraph	Please add SEC to the following sentence: The company claims similarity in administration, monitoring, disease management, and adverse event (AE) costs compared to IXE and SEC and therefore includes only drug acquisition costs in the cost-comparison model.	The current wording suggests that the company only claimed similarities to IXE, which is inaccurate.	Amended as suggested.
Page 11, Section 3.1	Please amend the following text to better reflect the warnings and contraindications present in current therapies and bimekizumab: “However, some patients with active axSpA, may not be suitable for treatment with BKZ. Contraindications for BKZ detailed in the company submission include patients with clinically significant active infections, including active tuberculosis. The European medical agency (EMA) has also advised that BKZ may increase the risk of infections such as upper respiratory tract infections and oral	The current wording is misleading, as warnings for URTI and candidiasis are shared by all IL17s, the warning against chronic and recurrent infection is shared by all b/tsDMARDs in axSpA, and the majority of therapies beyond NSAIDs have not allowed TB patients into trials out of caution.	Not a factual inaccuracy. Detail is required here as the EAG is describing the population likely to received treatment. For clarity, we have added the sentence below to the end of this paragraph: “Overall, contraindications for treatment with BKZ are

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	candidiasis, and it should be used with caution in patients with chronic infection or a history of recurrent infection. In addition to these contraindication, clinical advice to the EAG is that BKZ, as with other IL-17 inhibitors, would be used cautiously in patients with inflammatory bowel disease (IBD). Patients with previous and active IBD would not be given BKZ, and clinicians may also opt not to give it to patients with a known family history of the condition" This could be amended and shortened to simply state: "Contraindications are consistent with other IL17 inhibitors."		consistent with other IL17 inhibitors."
Page 25, Section 4.2.3.4, Paragraph 4	Please amend this statement: "In this appraisal the company explored placebo-adjustment in both FE and RE models although data sparsity means that RE placebo-adjusted models were not well estimated and should be discarded" Please amend to:	The current wording is inaccurate and implies the statement is true for all outcomes. RE PBO-adjusted fit well for several of the AS naive networks outcomes (CS; Table 27-30 of App D).	This is not referring to concerns with model fit, but to concerns with how much data are available. As previously noted, the EAG is focusing only on the subset of outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	"In this appraisal the company explored placebo-adjustment in both FE and RE models. Whilst the FE models provided the most reliable results for the majority of outcomes, RE placebo-adjusted models were appropriate for the ASDAS-CII and BASDAI50 outcomes in the AS pure naïve, and for ASAS20, ASDAS-CII, ASDAS-MI, and BASDAI50 outcomes in the AS predominantly naïve networks".		described in Section 4.2.3.3. Typical rules for estimability of parameters state that for RE models, at least 3 studies are required (ideally at least 5) on at least one comparison to adequately estimate the (shared) between-study heterogeneity, and for meta-regression at least 10 studies are needed for each regression coefficient being estimated, unless strong informative priors are given to these parameters. The naïve networks presented by the company are at the very lower limit of estimability of parameters.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			The fact that the regression parameter and/or the heterogeneity are inadequately estimated is demonstrated by the very wide CrIs for Beta for ASAS20 and BASDAI50 which also include zero (CS, Supplement 1, Table 43) For clarity the following text was added to this sentence: “In this appraisal the company explored placebo-adjustment in both FE and RE models although data sparsity means that RE placebo-adjusted models were not well estimated (95% credible intervals for the regression parameters were very

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			wide and included zero - CS Appendix D, Supplement 1) and should be discarded."
Page 25, paragraph 6	Please remove the following text: However, this suggests that the assumption of similar clinical efficacy across IL-17 inhibitors may not hold, which contradicts the central assumptions made in this cost-comparison	The current conclusion is incorrect. The conclusion in TA718 was based on networks containing less information than the networks presented here. This implies that new data does not require re-evaluating assumptions which contravenes NICE methodological guidance.	Not a factual inaccuracy. The EAG is describing an inconsistency between conclusions drawn in TA718 and what is being proposed in the current appraisal without making a judgement of which is correct.
Page 26, Section 4.2.3.5, Paragraph 4	Please amend the following statement: "However, the inappropriate exclusion of studies reflects the EAG's critique of the company's SLR in Section 4.1.1."	The current wording is misleading because it states that all of the excluded studies were inappropriately excluded. However, there are legitimate reasons to exclude the specified studies: • Barkham 2009: infliximab is not licensed for nr-axSpA by the EMA or FDA; the definition of nr-	Not a factual inaccuracy, the EAG is describing how study inclusion differs from previous appraisals. It is already acknowledged that exclusion of most of these studies does not have a major impact on the results of this

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		axSpA in the trial does not align with modern definitions which allow for diagnosis by signs and symptoms without MRI • Brandt 2003: Placebo patients switched treatment arms at 6 weeks such that all patients received ETN after the initial double-blind phase of the study. Thus the study did not meet the requirement of reporting relative treatment comparisons at between 12-16 weeks of randomised treatment. • Giardina 2010: Compared etanercept and infliximab. Inclusion of this study would not affect this appraisal. • Van den Bosch 2002: Only approximately 50%	appraisal (although some additional evidence from Giardina might have contributed to better estimation of RE or meta-regression models). For clarity this was amended to "However, the inappropriate exclusion of studies adds to ~~reflects~~ the EAG's critique of the company's SLR in Section 4.1.1."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		of patients are in the relevant indication, with the remaining 50% having psoriatic arthritis.	
Page 26, Section 4.2.3.5, Paragraph 5	Please amend the following text: "No studies included in the company's network diagrams report data for all outcomes". To: "No comparator studies included in the company's network diagrams report data for all outcomes."	The current wording is misleading and implies there is less data available than was actually included in the models; for example, BE MOBILE 1 in the nr-axSpA network reports data for all outcomes.	Amended as suggested.
Page 26, Section 4.2.3.5, Paragraph 6	Please remove the following text "In nr-axSpA, SEC could not be compared to BKZ for ASAS20, change from baseline in BASDAI and in BASFI, as there was no data for these outcomes."	The current wording implies BKZ could not be compared to SEC across all networks. However, this is only true for the purely naïve network and there are data for all of these outcomes in the predominantly naive network.	Amended as suggested.
Page 28, paragraph 1	Please remove the following text: "The company did not present the relative effect estimates from these models."	These data were available from the NMA reports.	The EAG could only find full NMA results (i.e., including relative effect estimates, not just model fit) for the company's preferred

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			models. For some relative effects presented in the NMA reports it is unclear which model they result from (it is unclear if placebo-adjusted models were used). NMA details including code were only made available to the EAG at a late stage. In addition, NMA code was only provided for the company's preferred models, not for all fitted models, despite request for full code at the clarification stage (question A8). The EAG was therefore unable to independently produce results for the EAG's preferred models.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 36, Paragraph 2, Sentence 1	In the following text, please either remove the phrase “claims to have” or provide additional information on how the dosing schedules in the submission differ from the relevant SmPCs. “The company claims to have sourced the dosing schedules for each treatment from the corresponding SmPCs, which are summarised in Table 5.”	The current wording implies that the company has not taken the dosing schedules from the relevant SmPCs, this is not accurate.	Amended to “The company states that ~~claims to~~ ~~have sourced~~ the dosing schedules for each treatment were sourced from the corresponding SmPCs, which are summarised in Table 5.”
Page 36, Paragraph 4, Sentence 2	Please amend: “The company stated that BE MOBILE 1 and BE- MOBILE 2 efficacy data for BKZ was selected to inform base-case analyses for simplicity, due to i) the underlying assumption of effectiveness equivalence across treatments and ii) response rate *“not typically (being) a model driver”* (response to clarification question B4).” To: “The company stated that BE MOBILE 1 and BE- MOBILE 2 efficacy data for BKZ was selected to inform base-case analyses for simplicity, due	The current wording implies that the company does not believe response rates to be a model driver in economic analyses of axSpA, this is not borne out in the company submission, so is factually inaccurate.	Amended as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	to i) the underlying assumption of effectiveness equivalence across treatments and ii) *"when all response rates are varied in the same direction and same magnitude for all comparators simultaneously, response rates are not typically a model driver"* (response to clarification question B4)".		
Page 40, Paragraph 3, Sentence 3	Please amend: "The company did not provide an analysis where treatment response was informed by pooled evidence for BKZ, SEC 150 mg and IXE, as requested by the EAG" To: "The company did not provide an analysis where treatment response was informed by pooled evidence for BKZ, SEC 150 mg and IXE, which was one of the approaches suggested by the EAG"	The current wording implies that UCB did not submit the requested analysis. Question B4 in the EAG clarification questions requested that UCB consider "Alternative sources of evidence (e.g., using trial data from SEC (150mg) and IXE trials, and/or using a pooled response rate for BKZ, SEC (150 mg) and IXE obtained by NMA)". UCB submitted analyses using the highest and lowest available response rates for IXE, SEC and BKZ, to provide 'bookend' analyses for the range of possible results. The approach	Amended to "The company did not provide an analysis where treatment response was informed by pooled evidence for BKZ, SEC 150 mg and IXE, which was one of the approaches suggested by the EAG at the clarification stage."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		suggested by the EAG would fall within this range. Varying treatment response data did not change model conclusions.	
Page 42, Paragraph 1, Sentence 4	Please amend: "This means that due to higher initial costs of loading SEC 150 mg compared to BKZ, longer time horizons will allow favour this drug when compared to BKZ." To: "This means that due to higher initial costs of loading IXE and SEC compared to BKZ, longer time horizons will favour these drugs when compared to BKZ."	The current wording does not acknowledge that a longer modelled time horizon favours IXE as well as SEC when compared to BKZ, given there are higher initial costs for both IXE and SEC.	Not a factual inaccuracy. IXE is not favoured in longer time horizons compared to BKZ. For clarity this was amended to: "This means that due to the higher initial costs of loading SEC 150 mg compared to BKZ, longer time horizons will ~~allow~~ favour this drug when compared to BKZ."

Issue 3 Additional context

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 8, paragraph 1	Please add an additional statement to the end of the following text to provide sufficient context: "A network meta-analysis could not be conducted for nr-axSpA b/tsDMARD-experienced patients due to these patients not being included in the clinical trials. Therefore, there is no evidence of comparative efficacy between BKZ, SEC 150 mg and IXE, for this sub-population. Therefore, comparisons in nr-axSpA should be based on the naïve population. This is consistent with TA383 where the conclusion was that the same efficacy modifiers from DANBIO could be applied to all intervention's naïve data in the absence of sufficient experienced data."	Additional context added to highlight that this approach is consistent with previous appraisals.	Not a factual inaccuracy. For clarity this was amended to: "A network meta-analysis could not be conducted for nr-axSpA b/tsDMARD-experienced patients due to these patients not being included in the clinical trials. Therefore, there is no evidence of comparative efficacy between BKZ, SEC 150 mg and IXE, for this sub-population. A similar lack of evidence has been noted in previous appraisals."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 8, paragraph 2	Please add an additional statement to the end of the following text to provide sufficient context: "Given that b/tsDMARD-experienced patients would be amongst those most likely to receive BKZ in clinical practice, the EAG consider the lack of reliable comparative evidence for these patients a key area of uncertainty. However, the company provided data from across the BKZ trial network in both Psoriasis and psoriatic patients (Clarification response question C2) demonstrating that bimekizumab is effective regardless of line of treatment and previous treatments, including previous TNF and previous IL17 exposure"	Depiction of UCB submission was not factually accurate. Additional context added to demonstrate the full extent of the company's submission.	This is not a factual inaccuracy. Whilst the additional evidence on other indications is valuable, evidence on the population of interest would be more reliable.
Page 8, Section 1.5	UCB suggest the statements below should be removed and replaced with a factual assessment of the data that UCB presented in the CS. The CS did not present any data on anti-drug antibodies, neutralising or otherwise, therefore this statement is factually inaccurate and should be removed. Please amend the	The CS presented 52 week data from the phase 3 BE MOBILE 1 and BE MOBILE 2 trials. UCB also presented 3 year safety and efficacy data from the phase 2b BE AGILE 1 trial and the BE AGILE 2 open label	Amended to: "Due to the limitations in long-term data, the long-term efficacy of BKZ in axSpA is a key area of uncertainty.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	following accordingly: Due to the limitations in long-term data, the long-term efficacy of BKZ in axSpA is uncertain. The CS reports patients developing anti-drug antibodies for BKZ which they classified as neutralising. However, anti-drug antibodies have been shown to hinder the activity/efficacy of the drug in long term. This is therefore a key area of uncertainty.	extension. Since submitting the CS, 5 year data from BE AGILE 2 study is available (14, 18). In analyses conducted using non-responder imputation at all time points, which assumes that patients with missing data are non-responders to treatment, these trials show that bimekizumab showed deep and durable response among the trials across several important clinical outcomes and consistent safety signals across the trial network out to 5 years on treatment (19, 20) (21-23) The CSRs for the clinical trials presented data on anti-drug antibodies, these results were descriptive (see BE MOBILE 1 CSR pp. 367 – 368, BE MOBILE 2 CSR p. 283, and BE AGILE 2 CSR p. 203) and do not validate a	

		cause and effect relationship between anti-drug antibodies and reduced treatment efficacy as implied by the EAG (14). To the contrary, the SmPC states that: "Across indications, no clinically meaningful impact on clinical response was associated with anti-bimekizumab antibodies development and an association between immunogenicity and treatment emergent adverse events has not been clearly established." The EPAR for axial spondyloarthritis immunogenicity analysis conclusions are in line with this (see EPAR, p. 74). Efficacy data for all patients, irrespective of antibody status are presented for all bimekizumab trials in the CS. The EAG and UCB do not have sufficient information to assess whether antibody	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		formation and maintenance of response are consistent across the comparators in this assessment.	
Page 12, Section 3,2	Please remove the following text to reflect the evidence provided by UCB during the clarification questions: "although IXE may lead to more injection site reactions"	As noted in the company response to clarification questions, IXE injection site reactions should be expected to decrease based on the introduction of the citrate free formulation that was approved by the EMA in December 2021 (11). In healthy participants, the citrate free formulation of IXE was associated with less injection site pain, and had no other notable differences in the safety profile compared with the original commercial formulation (24).	Not a factual inaccuracy. This is reflecting independent clinical advice to the EAG on their experience of current therapy on the NHS.
Page 18, Section 4.1.2	Please note, contrary to the following text, feasibility assessments for the NMAs were provided as appendices in the NMA	The feasibility assessments were available from the NMA reports.	Not a factual inaccuracy. We were unable to locate these documents within

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	reports (Appendix 2 in both the nr-axSpA and AS NMA reports). We therefore suggest the following text is removed: "However, the EAG could not identify details on the methods of this feasibility assessment and therefore are unable to critique its conduct."		the EAG's timelines for this appraisal. Multiple documents were submitted at different stages, with multiple layers of appendices, which were not clearly cross-referenced. The NMA reports were only made available to the EAG in a readable format at a late stage and the embedded additional documents are not clearly signposted in the main document as providing additional details. We were unable to review these (almost) "invisible" documents. For clarity this was amended to: "However, the EAG could not ~~identify~~ locate the details on the methods of this feasibility assessment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			and therefore were unable to critique its conduct during the timelines of this appraisal."
Page 20, paragraph 1	Please amend or remove the following statement to correct incorrect attribution of advisory board content presented in confidence by UCB: The EAG also note that [redacted] The EAG also note that during [redacted]	Additional context is required to specify this was the opinion of a single HTA expert, not of the clinicians. This statement also does not comply with NICE minimum reporting standards as the context of the statement cannot be provided without exposing in confidence data.	Not a factual inaccuracy. For clarity this was amended to: "The EAG ~~also~~ note that in the company's ~~own~~ clinical advisory board [redacted]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	[redacted]."		

Issue 4 Data and Figure errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 29, Figure 1 heading	Please make clear in the figure title which model is being presented. Please amend: "Figure 1. Treatment effect estimates for the company's preferred models for nr-axSpA" To: "Figure 1. Treatment effect estimates for the company's preferred models for nr-axSpA (fixed effect in the predominantly naïve network)"	Mislabelled figures may cause incorrect interpretation by the reader.	Amended to "Figure 1. Treatment effect estimates for the company's preferred models for nr-axSpA (predominantly naïve network)" The preferred models are described in Table 7 of the EAG report.
Page 29, Figure 1, BASDAI50	Please correct the values in BASDAI 50 ixekizumab and secukinumab to those found in Table 7 of the EAG report, as the currently presented values are a repeat of ASAS40:	Incorrect values presented.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	Current values: IXE: 1.6 (0.58, 3.52) SEC: 1.97 (0.95, 4.13) Amended values: IXE: 1.17 (0.47, 2.97) SEC: 1.46 (0.73, 3.11)		
Page 30, Figure 2 heading	As with Figure 1, please make clear in the figure title which model is being presented. Please add which model is being presented and whether it was placebo adjusted or not	Mislabelled figures may cause incorrect interpretation by the reader.	Not amended. Company's preferred models are described in table 7 of the EAG report.
Page 30, Figure 2	Please amend the following incorrect data values: Current values: Naïve, BASFI CFB, IXE: –0.09 (–0.57, 0.40) Experienced, ASAS20, IXE: 1.50 (0.50, 4.75) Amended values: Naïve, BASFI CFB, IXE: –0.09 (–0.57, 0.39)	Incorrect values presented.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	Experienced, ASAS20, IXE: 1.50 (0.35, 4.75)		
Page 32, Figure 3	Please make clear in the figure title which model is being presented. Please add which model is being presented and that these results were from the combined safety population. Figure 3. Results for NMAs conducted on safety and tolerability outcomes (fixed effect model, combined axSpA safety population)	Mislabelled figures may cause incorrect interpretation by the reader.	Amended to "Figure 3. Results for NMAs conducted on safety and tolerability outcomes (combined axSpA safety population)" Company's preferred models are described in table 7 of the EAG report.
Page 42, Paragraph 1, Sentence 2	Please amend: "This is because a higher number of doses is costed in the first model cycle for IXE (3 doses) and SEC (5 doses) compared to BKZ (3 doses)." To: "This is because a higher number of doses is costed in the first model cycle for IXE (3 doses) and SEC (5 doses) compared to BKZ (2 doses)."	Incorrect number of doses in the first model cycle stated for BKZ, which has 2 doses in the first model cycle.	Amended as suggested. This was a typographical error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 50, Table 7, AS, predominantly b/tsDMARD-naïve, Continuous MD (95% CrI), BASFI CFB	Please correct the IXE vs BKZ relative effect for BASFI CFB Placebo adjusted fixed effect from: –0.09 (–0.57, 0.399) To: –0.09 (–0.57, 0.39)	Incorrect data value.	Amended

Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, page 13, paragraph 4, second and third sentences	[redacted]	Please unmark in full. Confidential marking is not needed for this text	Unmarked.

References

1. National Institute for Health and Care Excellence (NICE). NICE Final Scope Bimekizumab for treating axial spondyloarthritis [ID6245]. Available at: https://www.nice.org.uk/guidance/gid-ta11347/documents/final-scope (accessed May 2023). 2023.
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