Comparative efficacy and safety of bimekizumab in axial spondyloarthritis: a systematic literature review and network meta-analysis

Atul Deodhar[1], Pedro M Machado[2], Michael Mørup[3], Vanessa Taieb[4], Damon Willems[5], Michelle Orme[6], David Pritchett[7], Lianne S Gensler[8]

1. Oregon Health & Science University, Portland, OR, USA
2. University College London, London, UK
3. UCB Pharma, Copenhagen, Denmark
4. UCB Pharma, Colombes, France
5. UCB Pharma, Brussels, Belgium
6. ICERA Consulting Ltd, Swindon, UK
7. Source Health Economics, London, UK
8. Department of Medicine/Division of Rheumatology, University of California, San Francisco, San Francisco, CA, USA

Corresponding author

Name: Atul Deodhar

Email address: deodhara@ohsu.edu

Postal address: Division of Arthritis and Rheumatic Diseases (OP09), Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR, 97239, USA

Abstract

Objectives: To compare the efficacy and safety of bimekizumab 160mg every 4 weeks, a selective inhibitor of interleukin-17F and 17A, with biologic/targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) in non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS).

Methods: A systematic literature review identified randomised controlled trials until January 2023 for inclusion in Bayesian network meta-analyses (NMAs), including three b/tsDMARDs exposure networks: predominantly-naïve, naïve, and experienced. Outcomes were Assessment of SpondyloArthritis international Society (ASAS)20, ASAS40, and ASAS partial remission (PR) response rates at 12–16 weeks. A safety NMA investigated discontinuations due to any reason and serious adverse events at 12–16 weeks.

Results: The NMA included 36 trials. The predominantly-naïve network provided the most comprehensive results. In the predominantly-naïve nr-axSpA analysis, bimekizumab had significantly higher ASAS20 response rates vs secukinumab 150mg (with loading dose [LD]/without LD), and comparable response rates vs other active comparators. In the predominantly-naïve AS analysis, bimekizumab had significantly higher ASAS40 response rates vs secukinumab 150mg (without LD), significantly higher ASAS-PR response rates vs secukinumab 150mg (with LD), and comparable response rates vs other active comparators. Bimekizumab demonstrated similar safety to other b/tsDMARDs.

Conclusion: Across ASAS outcomes, bimekizumab was comparable with most b/tsDMARDs, including ixekizumab, TNF inhibitors and upadacitinib, and achieved higher response rates vs secukinumab for some ASAS outcomes in predominantly b/tsDMARD-naïve nr-axSpA and AS patients at 12–16 weeks. In a pooled axSpA network, bimekizumab demonstrated comparable safety vs other b/tsDMARDs.

Keywords

Axial spondyloarthritis, Systematic literature review, Network meta-analysis, b/tsDMARDs, nr-axSpA, r-axSpA

Key messages

- Bimekizumab achieves higher response rates versus secukinumab for some ASAS outcomes in nr-axSpA and AS.
- Bimekizumab is associated with similar response rates versus other b/tsDMARDs across ASAS outcomes.
- Bimekizumab demonstrates similar safety and tolerability to other b/tsDMARDs.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that predominantly affects the axial skeleton (sacroiliac joints and spine) (1, 2). AxSpA comprises patients with evident radiographic damage to the sacroiliac joints (ankylosing spondylitis [AS], also known as radiographic axSpA [r-axSpA]) and those without definitive radiographic sacroiliitis (non-radiographic axSpA [nr-axSpA]) (3, 4). Age of disease onset is typically mid-twenties (5), with an estimated 10–40% of nr-axSpA patients progressing to AS over 2–10 years (6).

Historically, nr-axSpA emerged as a subclassification of axSpA; however, axSpA is now widely considered a single disease spectrum, encompassing both nr-axSpA and AS (7). AS and nr-axSpA share a similar clinical presentation and disease burden (8-10); both are associated with chronic back pain, fatigue, and morning stiffness, affecting mobility and the ability to perform daily activities (11, 12). Many patients with axSpA also have peripheral musculoskeletal manifestations, with peripheral arthritis and enthesitis most common (affecting an estimated 28–30% and 29–35% of patients, respectively) (13). Some patients also present with extra-musculoskeletal manifestations, including

acute anterior uveitis, psoriasis, and inflammatory bowel disease (12, 14-16). As such, axSpA has a considerable impact on quality-of-life (17-20).

The initial pharmacological treatment for axSpA is non-steroidal anti-inflammatory drugs (NSAIDs). For patients with active disease and an inadequate response, intolerance, or contraindication to NSAIDs, available therapies include biologic disease-modifying anti-rheumatic drugs (bDMARDs), comprising tumour necrosis factor (TNF) inhibitors, interleukin (IL)-17A inhibitors, and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs) like the recently approved Janus kinase (JAK) inhibitors (21, 22).

Despite available treatments, many patients do not achieve a sufficient treatment response or partial remission, and some lose their clinical response to treatment over time (23, 24). Furthermore, clinical response to second-line bDMARDs is lower than in bDMARD-naïve patients (25); hence, there is a considerable need for treatment options achieving deep and sustained responses via a novel mechanism of action (23, 24).

Bimekizumab is a humanised monoclonal immunoglobulin G1 antibody that recently received marketing authorization in EU and UK, and that selectively inhibits interleukin (IL)-17F in addition to IL-17A. Interleukin-17A and IL-17F are pro-inflammatory cytokines and key mediators of inflammation and new bone formation which leads to structural damage in axSpA (26-28). Unlike IL-17A-specific inhibitors, bimekizumab enables neutralisation of IL-17F/F in addition to IL-17A/A and IL-17A/F. Preclinical data demonstrate that dual blockade of IL-17A and IL-17F is required for optimal inhibition of downstream inflammatory and tissue remodelling responses (30). In the Phase III trial programme for axSpA, bimekizumab resulted in significant and rapid improvements in efficacy outcomes vs placebo (BE MOBILE 1 [NCT03928704] and BE MOBILE 2 [NCT03928743]) (31).

The aim of this analysis was to establish the comparative efficacy, safety, and tolerability of subcutaneous (SC) bimekizumab 160 mg every 4 weeks (Q4W) versus b/tsDMARDs in axSpA using a systematic literature review (SLR) and Bayesian network meta-analyses (NMA). The current

analysis provides an up-to-date synthesis of available evidence, including the BE MOBILE studies (31), which were published since the completion of previous SLRs/NMAs in axSpA. Although TNF inhibitors were included in the analysis, the relative efficacy of these is already well-established (32, 33), so this NMA focuses on comparisons between recently approved IL-17A, IL-17A/F, and JAK inhibitors.

Methods

Systematic literature review

A clinical SLR was initiated in May 2012 and updated eight times, most recently on 10th January 2023, to identify randomised controlled trial (RCT) evidence assessing bimekizumab and relevant b/tsDMARDs for the treatment of adult patients with AS or nr-axSpA with an inadequate response to, intolerance of, or contraindication to NSAID therapy (see Supplementary Data S1 for dates of all SLR updates, available at *Rheumatology* online). Studies were required to report outcome measurements after a minimum of 12 weeks of follow-up, but before switch/cross-over or early escape (34, 35). Eligible interventions comprised IL-17A inhibitors, IL-17A/F inhibitors (i.e. bimekizumab), TNF inhibitors, and JAK inhibitors. Eligible comparators comprised any of the aforementioned interventions, conventional DMARDs, NSAIDS, or placebo. The pre-specified population, intervention, comparator, outcomes, and study design (PICOS) elements used to assess study eligibility are presented in Supplementary Table S1, available at *Rheumatology* online.

The SLR was performed in accordance with best practice guidelines from the Cochrane Collaboration, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the Centre for Reviews and Dissemination (CRD) (36-38). The Ovid platform was used to search Embase, MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews (CDSR) on 10th January 2023. Electronic database search strings were developed for Embase, then translated for the other databases to account for differences in syntax and subject headings (Supplementary Table S2–S4, available at *Rheumatology* online). Title/abstract screening and full-text screening were both performed by two independent reviewers.

Any conflicts regarding eligibility were resolved through discussion, and where necessary, arbitration was provided by a third reviewer. Hand-searching of conference proceedings, HTA submissions, clinical trial registries, and the reference lists of relevant SLRs/NMAs were used as supplementary measures to ensure all relevant studies were captured (Supplementary Data S2, available at *Rheumatology* online). Relevant unpublished clinical study reports for bimekizumab were also eligible for inclusion. Data extraction and risk of bias assessment were performed by one reviewer, with all datapoints and risk of bias judgments checked by a second independent reviewer. Risk of bias was assessed using the CRD 7-item checklist for RCTs, currently recommended by the National Institute for Health and Care Excellence (NICE) (39).

NMA feasibility assessment

Additional eligibility criteria (Supplementary Table S5, available at *Rheumatology* online) were applied to identify studies suitable for inclusion in the NMA. Licensed b/tsDMARDs were the comparators of primary interest. Reasons for exclusion from the NMA included atypical axSpA classification criteria, biosimilar studies, and treatments with limited licensing or for which the development programme has been terminated. While secukinumab can be increased from 150 mg to 300 mg in clinical practice, the 300 mg dose could not be included in the NMA due to insufficient trial data on the approved SC 300 mg dose (40). Although the MEASURE 3 trial reports data for secukinumab 300 mg SC Q4W at week 16, loading was by intravenous (IV) infusion, which is currently not approved.

Network meta-analysis

For efficacy outcomes, separate Bayesian NMAs were performed for patients with nr-axSpA and AS. Analyses were performed for three subpopulations, defined by patients' prior b/tsDMARD exposure:

- **Predominantly (>50%) b/tsDMARD-naïve network:** Studies where >50% of the enrolled patients were b/tsDMARD-naïve or where it can be assumed that >50% of patients were b/tsDMARD-naïve.
- **100% b/tsDMARD-naïve network:** Studies where either 100% of the enrolled patients were b/tsDMARD-naïve or where studies reported separate data for a b/tsDMARD-naïve subgroup.

- **100% b/tsDMARD-experienced network:** Studies where either 100% of the enrolled patients were b/tsDMARD-experienced or where studies reported separate data for a b/tsDMARD-experienced subgroup.

Based on the timepoint at which the included studies reported primary and secondary efficacy results, the timepoint used for the NMA was 12–16 weeks; for inclusion in the NMA, studies had to report outcomes after a minimum of 12 weeks of follow-up (41), but before switch/cross-over or early escape. ASAS-defined improvement criteria (used in clinical trials) of interest for the efficacy NMA were ASAS20, ASAS40, and ASAS-PR (Table 1).

Two tolerability and safety outcomes at week 12-16 were also analysed: discontinuation due to any reason, and serious adverse events (SAEs). These analyses were conducted in a combined nr-axSpA and AS population irrespective of previous TNF exposure, due to the small number of patients experiencing events, and because patient characteristics and dose exposure of treatments were similar across the two indications.

Bimekizumab was compared to both placebo and active comparators. Doses for bDMARD comparators included in the NMA were:

- IL-17A inhibitors: ixekizumab 80 mg Q4W SC, secukinumab 150 mg Q4W SC (some patients may first receive initial loading doses (LDs) of secukinumab 150 mg SC at Weeks 0, 1, 2, 3 and 4 followed by Q4W thereafter; herein referred to as ‘with LD’ or ‘without LD’, respectively).

- IL-17A/F inhibitors: bimekizumab 160 mg Q4W.

- TNF inhibitors: adalimumab 40 mg twice-weekly (Q2W) SC, certolizumab pegol 200 mg Q2W or 400 mg Q4W SC, etanercept 25 mg BIW or 50 mg QW SC, golimumab 50 mg Q4W SC or 2mg/kg Q8W IV, infliximab 5 mg IV Q6W. TNF inhibitors were pooled as a single treatment class because the relative efficacy of TNF inhibitors in axSpA is already well-

established (42, 43). Moreover, HTA publications, such as NICE TA383, conclude that TNF inhibitors should be considered as a single class with broadly similar effects (44).

Doses for tsDMARD comparators were:

- JAK inhibitors: upadacitinib 15 mg once-daily (QD) oral, tofacitinib 5 mg twice-daily (BID) oral (AS only).

Statistical analysis

A Bayesian framework was chosen for the NMAs as Bayesian analysis is a standard approach that has been extensively used by researchers due to the fact that, as described in the NICE Decision Support Unit (DSU) guidance, "simulation from a Bayesian posterior distribution supplies both statistical estimation and inference, and a platform for probabilistic decision making under uncertainty" (45). The NMAs were conducted using standard methods for clinical data synthesis in WinBUGs using validated model code for binomial outcomes, using a binomial model with logit link, available from the NICE DSU (45-49, 51, 52, 54, 55). The WinBUGs models were run for a minimum burn-in of 10,000 iterations to maximise convergence. Subsequently, three chains of at least 1,000 samples (3,000 simulations) were drawn from the posterior distributions. Both random and fixed effect, and unadjusted and placebo-adjusted models were fitted to the data, with the mean residual deviance and the deviance information criteria (DIC) used to estimate how well the predicted values fitted the observed dataset. An alternative form of the DIC was also estimated (total residual deviance + posterior variance) as for some analyses, the number of effective parameters was estimated to be negative (56). However, this parameter did not always differentiate between models and other factors, such as poor convergence or unrealistically large credible intervals (CrIs), would eliminate a particular model. Fixed-effect (nr-axSpA; combined axSpA) and fixed effect placebo-adjusted (AS) models offered preferred model fit. Results are expressed as odds ratios (ORs). Significant differences between treatments were based on the 95% CrI for the OR crossing 1. Surface under the cumulative ranking curve (SUCRA) values were calculated for each treatment, with higher values representing

higher ranked treatments (57). Note that SUCRA values should not be considered in isolation but interpreted alongside OR point estimates and CrIs (57).

Results

Systematic literature review

Overall, 341 publications reporting on 65 unique trials were included in the SLR (Figure 1 and Supplementary Figures S1 and S2, available at *Rheumatology* online); the feasibility assessment determined that 36 trials were suitable for inclusion in this NMA, comprising 10 in nr-axSpA, and 27 in AS (note one reported separate data for both populations [RAPID-axSpA (10)]). Baseline patient and disease characteristics of the included studies are provided in Supplementary Tables S6–S9, available at *Rheumatology* online. Reasons for exclusion of the 29 remaining trials are provided in Supplementary Table S10, available at *Rheumatology* online. Trials were broadly similar in terms of their main baseline characteristics (where reported). Enrolment of patients with nr-axSpA was based on meeting the 2009 ASAS axSpA classification criteria (58), with the presence of objective signs of inflammation defined by bone marrow edema on magnetic resonance imaging (MRI) and/or elevated C-reactive protein (CRP). For most AS trials (24 of 27) enrolment of patients was based on the 1984 modified New York (mNY) criteria (59). However, the entry criteria for three studies (COAST-V, COAST-W, and Xue 2022) restricted patients to those meeting the more recent ASAS classification criteria (58), which uses the imaging criterion of the mNY criteria for radiographic axSpA plus additional criteria (>1 feature of axSpA). Agreement between the mNY and ASAS r-axSpA criteria is reported to be very high (4) and these populations are likely to have considerable clinical overlap, despite differences in classification. In BE MOBILE 2, patients were enrolled with mNY criteria, and met ASAS criteria for the classification of r-axSpA. It was therefore assumed that the trial populations were sufficiently similar to be directly compared in the NMA.

The risk of bias for individual trials included in the NMA is provided in Supplementary Table S11, available at *Rheumatology* online. Overall, the included RCTs had a low risk of bias, with some elements of the assessment ranking unclear due to missing reporting. One area of weakness was that a

small number of baseline characteristics differed across the randomised treatment groups within five AS trials and one nr-axSpA trial (60-65). However, no studies were deemed unsuitable for inclusion in the NMA based on concerns regarding risk of bias.

The network diagram for the predominantly b/tsDMARD-naïve networks (in nr-axSpA and AS) are presented in Figure 2. The 100% b/tsDMARD-naïve, experienced (for efficacy) and combined axSpA population (tolerability and safety) networks are provided in Supplementary Figure S3–S5, available at *Rheumatology* online.

Network meta-analysis

Predominantly (>50%) b/tsDMARD-naïve network

The predominantly b/tsDMARD-naïve network provided the most comprehensive results across outcomes and comparators comprising all 10 nr-axSpA studies and 25 out of 27 AS studies. Across the network, approximately 90% of patients were b/tsDMARD-naïve (67%–100% naïve in nr-axSpA and 61%–100% naïve in AS).

ASAS20

Ten nr-axSpA studies and 24 AS studies reported ASAS20 (Supplementary Table S12 and S13, available at *Rheumatology* online). In nr-axSpA, bimekizumab was associated with significantly higher ASAS20 versus secukinumab 150 mg Q4W without LD (OR 2.18, 95% CrI: 1.13, 4.24) and secukinumab 150 mg Q4W with LD (OR 2.31, 95% CrI: 1.20, 4.53). Bimekizumab was comparable with all other active comparators; no further significant differences between bimekizumab and active comparators were observed. In AS, bimekizumab was associated with similar ASAS20 response rates compared with other active treatments in AS (Figure 3). Predicted probabilities for ASAS20 response by treatment are presented in Figure 4 and relative risk (RR) estimates for bimekizumab compared with other b/tsDMARDs are presented in Supplementary Table S14, available at *Rheumatology* online.

ASAS40

Ten nr-axSpA studies and 22 AS studies reported ASAS40 (Supplementary Table S12 and S13). In nr-axSpA, bimekizumab was associated with similar (95% CrI crosses 1.0) ASAS40 response rates compared with other active treatments. In AS, ASAS40 response rate was significantly higher with bimekizumab in AS versus secukinumab 150 mg Q4W without LD (OR 1.60, 95%CrI: 1.01, 2.60). No other significant differences between bimekizumab and active comparators were observed (Figure 3). Predicted probabilities for ASAS40 response by treatment are presented in Figure 4 and RR estimates for bimekizumab compared with other b/tsDMARDs are presented in Supplementary Table S14.

ASAS-PR

Nine nr-axSpA studies and 16 AS studies reported ASAS-PR (Supplementary Table S12 and S13). In nr-axSpA, bimekizumab was associated with similar ASAS-PR response rates compared with other active treatments. In AS, bimekizumab was associated with significantly higher ASAS-PR compared with secukinumab 150 mg with LD (OR 1.65, 95% CrI: 1.08, 2.51) and similar ASAS-PR response rates compared with the other active treatments in AS (Figure 3). Predicted probabilities for ASAS-PR response by treatment are presented in Figure 4 and RR estimates for bimekizumab compared with other b/tsDMARDs are presented in Supplementary Table S14.

No other significant differences between bimekizumab and active comparators were observed in the predominantly b/tsDMARD-naïve network. League tables of pairwise comparisons for all treatments in the predominantly b/tsDMARD-naïve network are presented in Supplementary Tables S15–S20, available at *Rheumatology* online.

100% b/tsDMARD-naïve network

Results of the 100% b/tsDMARD-naïve network were broadly consistent with results of the predominantly b/tsDMARD-naïve network; no significant differences between bimekizumab and active comparators were observed for any outcome (Supplementary Table S21, available at *Rheumatology* online).

100% b/tsDMARD-experienced network

Two AS studies enrolled 100% b/tsDMARD-experienced patients (COAST-W and SELECT-AXIS 2 [Study 1]) and a further seven AS studies reported data for the subgroup of b/tsDMARD-experienced patients enrolled in the trial (Supplementary Table S13). These nine AS studies were included in the 100% b/tsDMARD-experienced analysis for ASAS20 and ASAS40. Seven of these studies also reported ASAS-PR for this subgroup; however, the analysis did not converge as there were too few patients in the subgroup and zero events in some of the placebo-control arms. No significant differences between bimekizumab and active comparators were observed for any outcome (Table 2). A b/tsDMARD-experienced network was not feasible in nr-axSpA as too few studies reported data for b/tsDMARD-experienced patients.

Combined axSpA population safety network

The combined axSpA population network for discontinuation due to any reason and for SAEs included 25 and 24 studies, respectively (Supplementary Table S22, available at *Rheumatology* online). Bimekizumab demonstrated comparable discontinuations due to any reason and comparable SAEs, relative to all active treatments in the network (Supplementary Table S23 and S24, available at *Rheumatology* online).

Discussion

This SLR and NMA provides an up-to-date synthesis of available evidence to determine the relative efficacy, tolerability, and safety of bimekizumab compared with b/tsDMARDs in adult patients with nr-axSpA or AS with an inadequate response to, intolerance of, or contraindication to NSAID therapy. Separate analyses were undertaken across three ASAS efficacy outcomes in the following patient subpopulations: predominantly (>50%) b/tsDMARD-naïve, 100% b/tsDMARD-naïve, and 100% b/tsDMARD-experienced. Tolerability and safety analyses were conducted in a combined axSpA population.

Prior to the approval of IL-17A and JAK inhibitors for axSpA, treatment options were relatively limited, with TNF inhibitors being the only available targeted therapies (21, 22). Today, a wider range

of treatments are available. The comparative efficacy of available b/tsDMARDs is of great interest to patients, clinicians, and payers alike; it is important to understand the relative efficacy of available therapies to determine best practices. Several placebo-controlled RCTs demonstrate the efficacy of recently available therapies, but head-to-head trials are lacking, and so NMA can assist in assessing their comparative effectiveness (66). Whilst previous NMAs in axSpA evaluated the relative efficacy of some therapies (42, 67-75), this is the first analysis that incorporates upadacitinib and bimekizumab.

The predominantly bDMARD-naïve network provided the most complete set of results across outcomes and comparators. In nr-axSpA, bimekizumab was associated with significantly higher ASAS20 response rates vs secukinumab 150 mg (in both the with and without LD comparisons), and in AS, ASAS40 and ASAS-PR response rates were significantly higher with bimekizumab vs secukinumab 150 mg without LD and secukinumab 150 mg with LD, respectively. Besides these comparisons, no significant differences were found; bimekizumab was associated with similar response rates compared with all other b/tsDMARDs.

Inclusion of recent Phase III trials of bimekizumab (BE MOBILE 1 and BE MOBILE 2 (76, 77)) enabled analysis of 100% b/tsDMARD-naïve and experienced subpopulations. Broadly, conclusions of the 100% b/tsDMARD-naïve network were consistent with those of the predominantly b/tsDMARD-naïve network, so the latter can be used as a proxy for the former (78). Importantly, the predominantly-naïve network used a more robust dataset (intention-to-treat/full analysis set) than an analysis using subgroup data, allowing more comparators to be included in the networks. In the 100% b/tsDMARD-experienced network, analyses were possible in AS for ASAS20 and ASAS40, and no significant differences between bimekizumab and active comparators were observed. These b/tsDMARD-experienced analyses are a novel addition to the literature, albeit with low trial and patient numbers, and should be interpreted with caution. Additionally, the safety and tolerability of bimekizumab at week 12-16 was comparable to all active comparators in the combined axSpA population.

To the best of our knowledge, this research represents the most recent and comprehensive SLR/NMA for axSpA, building upon previous meta-analyses in b/tsDMARD-naïve patients (44, 69, 73-77). A 2018 NMA published by Deodhar et al compared the efficacy of TNF, IL-17, and JAK inhibitors (tofacitinib only) in AS . The authors concluded that tofacitinib, golimumab IV, and infliximab had the highest SUCRA values for efficacy; however, differences in efficacy were not significantly different and analyses were based on one small Phase II study for tofacitinib . The current analysis includes Phase III trials for bimekizumab (58) and JAK inhibitors (78-80) which were not available at the time of the previous NMA, as well as data for nr-axSpA. The present analysis also includes new outcomes relative to the Deodhar study, including ASAS40, ASAS-PR, and safety/tolerability outcomes. For ASAS20, the only outcome included in both studies, results in the predominantly-naïve network were consistent with those previously published, with bimekizumab now featuring amongst the most efficacious treatments.

Limitations

Whilst some baseline characteristics differed between studies, no studies were deemed unsuitable for inclusion in the NMA based on differences in baseline characteristics, and the overall risk of bias was low. However, for 100% b/tsDMARD-naïve and experienced analyses, some evidence comes from trial subgroup data for which baseline characteristics are not available; this introduces uncertainty regarding how balanced the study arms are. Results are based on fixed-effect (nr-axSpA; combined axSpA) and fixed-effect placebo-adjusted (AS) models, which may underestimate uncertainty in the treatment effects. However, these results estimated some wide 95% CrIs for the relative treatment effects, even using the fixed-effect models, and thus additional clinical study data would be beneficial to reduce the uncertainty in the findings. Any additional study data would also help to enable a more rigorous assessment of between-study heterogeneity and placebo-effects adjustment. There is a paucity of RCT data for b/tsDMARD-experienced patients, and this network was not feasible in nr-axSpA. Nine studies reported data for this subgroup subpopulation in AS, leading to a network of eight treatments (including placebo). For the b/tsDMARD-experienced network, the comparisons against bimekizumab were based on subgroup data from BE MOBILE 2; however, 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 . The placebo arm of BE MOBILE 2, that connects to the rest of the network, contained just 17 patients, and so the analysis is subject to uncertainty. The safety analyses are also associated with increased uncertainty due to the small number of events. Further limitations of the NMA include different ages of included studies (2002 [infliximab] to 2022 [ixekizumab] (81, 82)), short-term efficacy analyses (12–16 weeks), and the lack of published data on 300 mg secukinumab, which prevented inclusion of this higher secukinumab dose in the NMA.

Conclusion

Across ASAS outcomes, bimekizumab demonstrated comparable efficacy with most b/tsDMARDs, including ixekizumab, TNF inhibitors and upadacitinib, and achieved higher response rates compared with secukinumab at 12–16 weeks for ASAS20 in predominantly b/tsDMARD-naïve nr-axSpA patients, and for ASAS40 and ASAS-PR in predominantly b/tsDMARD-naïve AS patients. In a pooled axSpA network, bimekizumab demonstrated comparable safety compared with other b/tsDMARDs. Overall, the present analyses provide evidence for bimekizumab being an efficacious option in the management of both b/tsDMARD-naïve and experienced patients across the axSpA spectrum, with similar safety and tolerability to existing treatments.

Conflict of Interest: D. Pritchett and M. Orme are employees of Source Health Economics and ICERA Consulting Ltd, respectively, the consultancy companies that conducted the systematic literature review and network meta-analysis (funded by UCB Pharma). M. Mørup, V. Taieb, and D. Willems are employees of UCB Pharma. D. Willems and V. Taieb are shareholders in UCB Pharma. A. Deodhar has received honoraria from AbbVie, Amgen, Aurinia, Bristol Myers Squibb, Eli Lilly, Janssen, MoonLake, Novartis, Pfizer, and UCB; and research grants from AbbVie, Bristol Myers Squibb, Celgene, Eli Lilly, Galvani, Janssen, MoonLake, Novartis, Pfizer, and UCB. P.M. Machado has received honoraria from AbbVie, BMS, Celgene, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche and UCB, all unrelated to this manuscript, and is supported by the National Institute for Health Research (NIHR), University College London Hospitals (UCLH), Biomedical Research Centre (BRC). L.S. Gensler has received honoraria from AbbVie, Acelyrin, Eli Lilly, Janssen, Novartis, Pfizer, and UCB, and research grants support from Novartis and UCB all unrelated to this manuscript.

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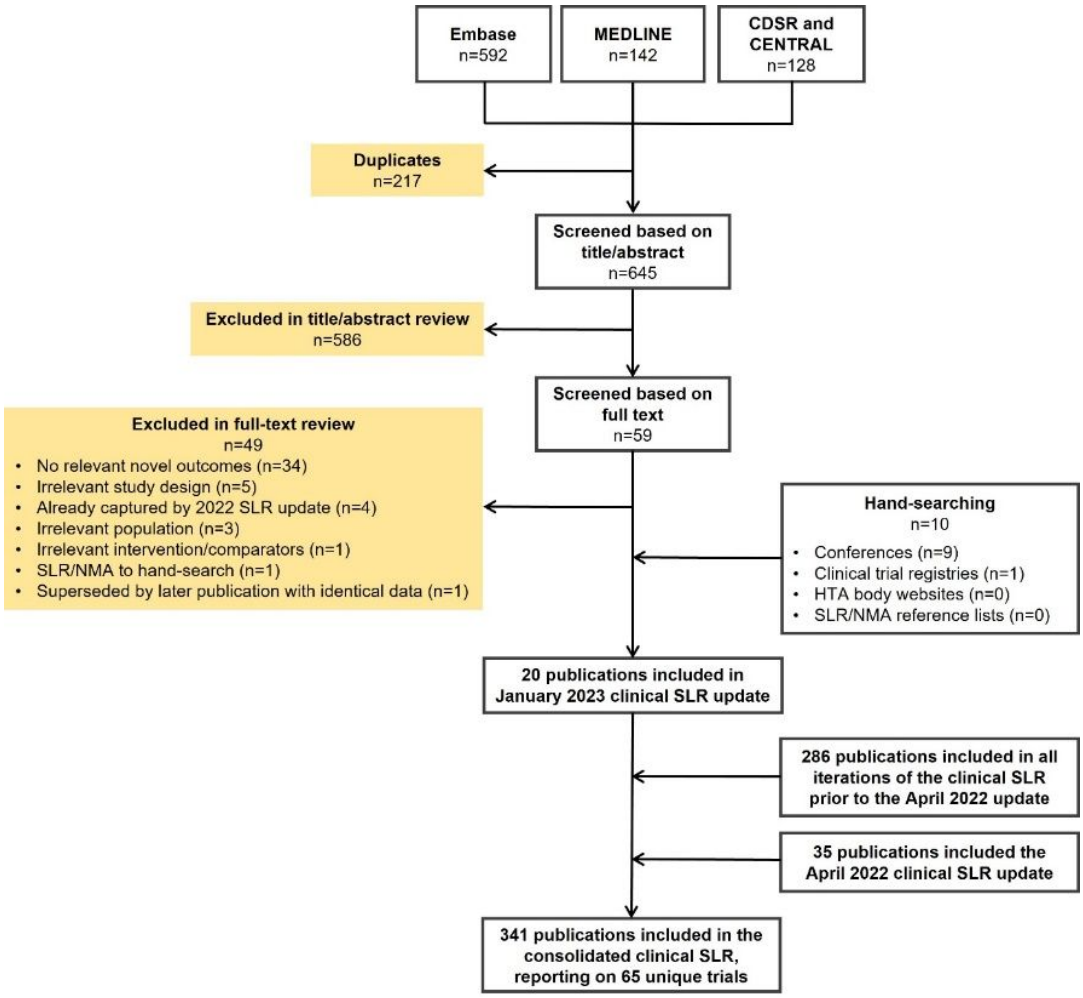
Tables and figures

Table 1: Outcomes included in the NMA

Outcome	Definition
ASAS20 and ASAS40	ASAS20 and ASAS40 represent a relative improvement from baseline of ≥20% and ≥40%, respectively, together with a predefined absolute improvement from baseline in three or more of the following domains: • Patient global assessment • Spinal pain (BASDAI question 2) • Function (BASFI) • Inflammation (mean of BASDAI questions 5 and 6 on morning stiffness) ASAS20 and ASAS40 are benchmarks for measuring symptomatic improvement in patient disease status in clinical trials, and are the primary outcomes of interest in many comparator trials in the NMA .
ASAS-PR	ASAS-PR is defined as <2 on a scale of 0–10 in each of the four ASAS domains : • Patient global assessment • Spinal pain (BASDAI question 2) • Function (BASFI) • Inflammation (mean of BASDAI questions 5 and 6 on morning stiffness) ASAS-PR corresponds to a state of partial remission/very low levels of disease activity and is also useful for cross-trial comparisons (86, 87). It is one of the most stringent clinical endpoints for axSpA; despite currently available treatments, many patients do not currently achieve a sufficient treatment response or very low levels of disease activity (23, 24, 83).

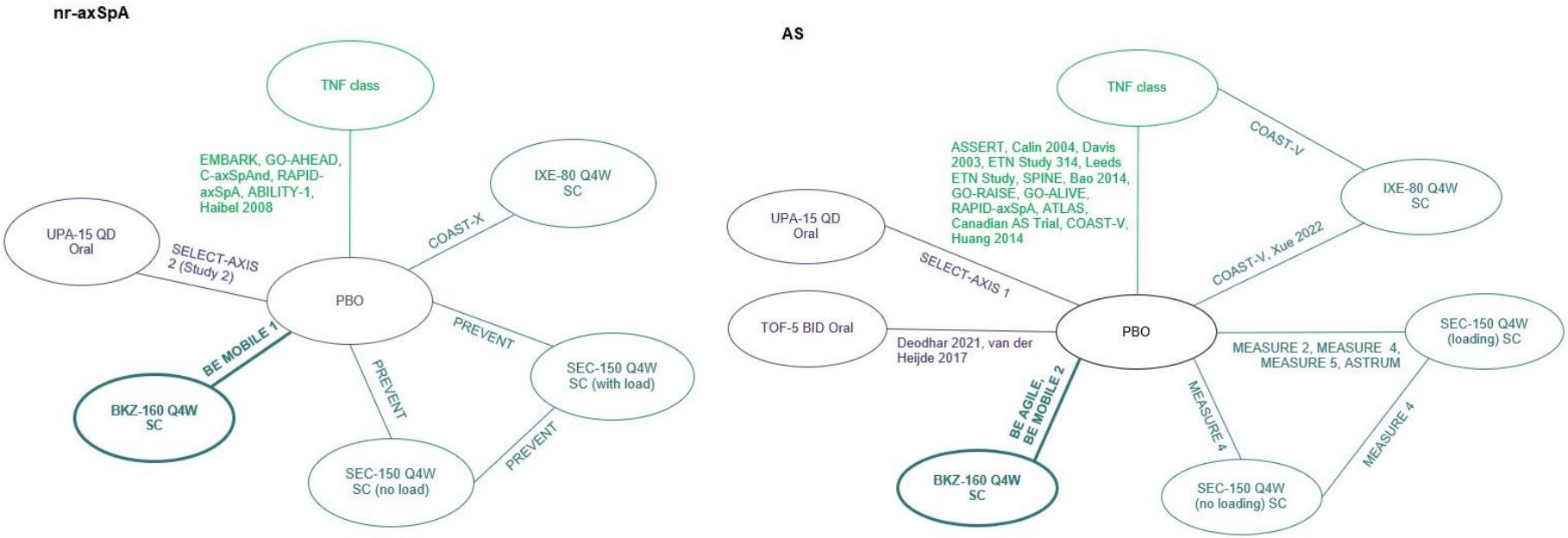
Abbreviations: ASAS20, Assessment of Spondyloarthritis international Society-improvement of ≥20%; ASAS40, Assessment of Spondyloarthritis international Society-improvement of ≥40%; ASAS-PR, Assessment of Spondyloarthritis international Society partial remission; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity index; BASFI, Bath Ankylosing Spondylitis Functional Index; NMA, network meta-analysis.

Figure 1: PRISMA flow diagram of SLR study selection



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; HTA, health technology assessment; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Figure 2: Network diagrams in nr-axSpA and AS (predominantly b/tsDMARD-naïve network)[a, b, c]



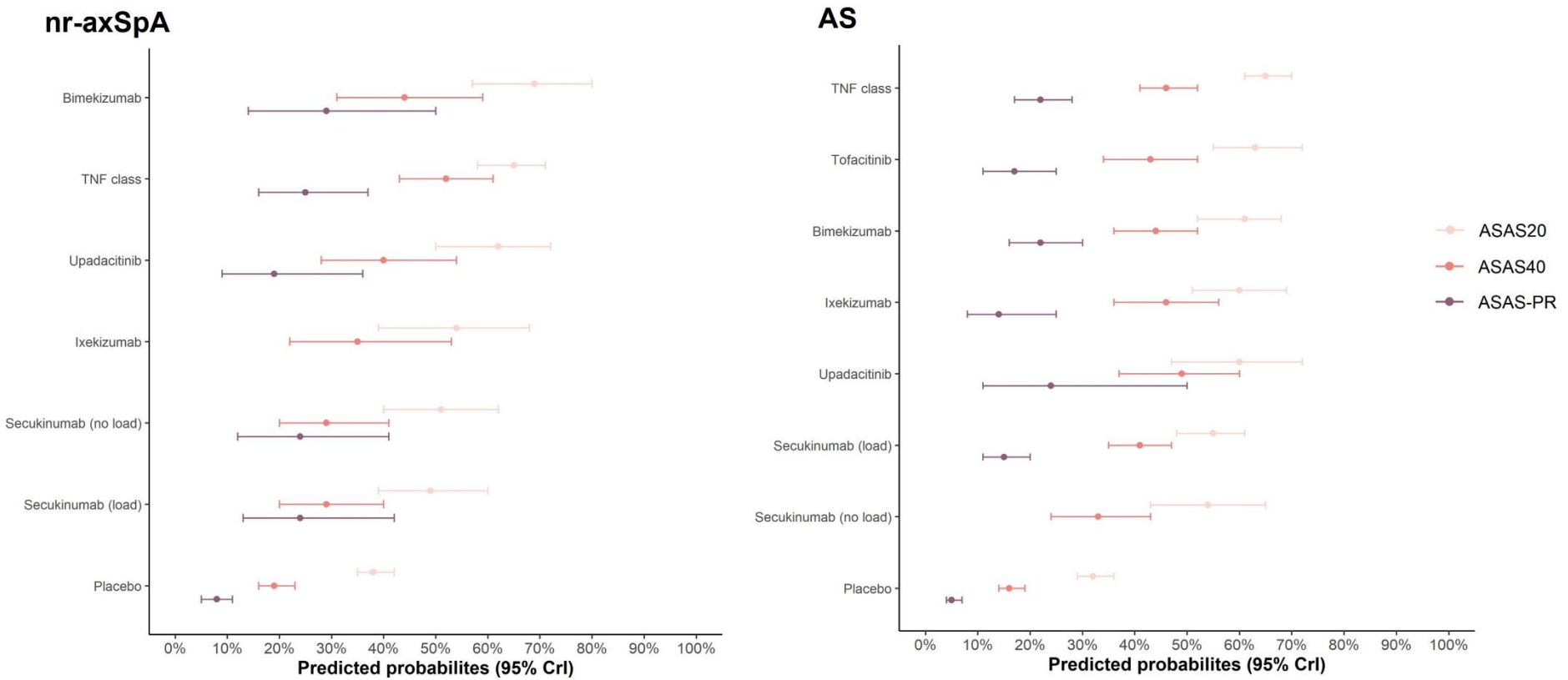
a Presented network diagrams are all studies that are included in one or more of the predominantly b/tsDMARD-naïve analysis; b See Supplementary Table S12 and S13 for list of studies that report ASAS20, ASAS40 or ASAS-PR outcome; c Network diagrams for 100% b/tsDMARD-naïve and experienced networks are provided in Supplementary Figure S3–S5.
Abbreviations: AS, ankylosing spondylitis; ASAS20, Assessment of Spondyloarthritis international Society-improvement of ≥20%; ASAS40, Assessment of Spondyloarthritis international Society-improvement of ≥40%; ASAS-PR, Assessment of Spondyloarthritis international Society partial remission; BID, twice-daily; BKZ, bimekizumab; b/tsDMARD, biologic/targeted synthetic disease-modifying anti-rheumatic drugs; IXE, ixekizumab; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; Q4W, every 4 weeks; QD, once-daily; SC, subcutaneous; SEC, secukinumab; TNF, tumour necrosis factor; TOF, tofacitinib; UPA, upadacitinib.

Figure 3: ASAS20, ASAS40, and ASAS-PR outcomes in predominantly b/tsDMARD-naïve patients with nr-axSpA and AS[a]

a Results expressed as ORs; higher ORs indicate better outcomes for bimekizumab. Bold denotes significance based on 95% CrI.

Abbreviations: ASAS, Assessment in Spondyloarthritis International Society; AS, ankylosing spondylitis; b/tsDMARD, biologic/targeted synthetic disease-modifying anti-rheumatic drugs; CrI, credible interval; nr-axSpA, non-radiographic axial spondyloarthritis; OR, odds ratio; PR, partial remission; SUCRA, surface under the cumulative ranking curve; TNF, tumour necrosis factor.

Figure 4: Predicted probabilities of response in nr-axSpA and AS (predominantly b/tsDMARD-naïve network), ranked by ASAS20



Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment in Spondyloarthritis International Society; b/tsDMARD, biologic/targeted synthetic disease-modifying anti-rheumatic drugs; CrI, credible interval; IV, intravenous; nr-axSpA, non-radiographic axial spondyloarthritis; PR, partial remission; SC, subcutaneous; TNF, tumour necrosis factor.

Table 2: NMA results in 100% b/tsDMARD-experienced network in AS only, bimekizumab vs comparator [a, b, c]

Treatment	ASAS20		ASAS40		ASAS-PR	
	OR (95% CrI)	SUCRA	OR (95% CrI)	SUCRA	OR (95% CrI)	SUCRA
Bimekizumab	Reference	66%	Reference	65%	Analysis did not converge - too few b/tsDMARD-experienced patients/zero events in control arm	
TNF inhibitor class[d]	1.30 (0.11, 6.50)	52%	0.70 (0.17, 2.35)	83%		
Upadacitinib	0.82 (0.28, 2.95)	81%	0.85 (0.40, 1.78)	78%		
Tofacitinib	1.85 (0.07, 11.39)	35%	1.71 (0.50, 5.21)	35%		
Ixekizumab	1.50 (0.35, 4.75)	40%	1.94 (0.83, 4.43)	28%		
Secukinumab (load)	1.13 (0.36, 3.93)	58%	0.86 (0.39, 1.87)	77%		
Secukinumab (no load)	1.05 (0.28, 4.51)	62%	1.87 (0.65, 5.30)	31%		
Placebo	2.91 (0.93, 8.51)	6%	**3.46 (1.67, 6.88)**	2%		

a Results expressed as ORs; higher ORs indicate better outcomes for bimekizumab. Bold denotes significance based on 95% CrI; b Network not feasible for nr-axSpA; c NMA based on 3 chains of 1,000 simulations; d Includes certolizumab pegol only.

Abbreviations: AS, ankylosing spondylitis; ASAS20, Assessment of Spondyloarthritis international Society-improvement of ≥20%; ASAS40, Assessment of Spondyloarthritis international Society-improvement of ≥40%; ASAS-PR, Assessment of Spondyloarthritis international Society partial remission; b/tsDMARD, biologic/targeted synthetic disease-modifying anti-rheumatic drugs; Crl, credible interval; NMA, network meta-analysis; OR, odds ratio; SUCRA, surface under the cumulative ranking curve; TNF, tumour necrosis factor.