EAG Final Report

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Upadacitinib for treating active non-radiographic axial spondyloarthritis [ID3958]: EAG final cost comparison report (updated following company factual accuracy check and confidential information check)

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UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Upadacitinib for treating active non-radiographic axial spondyloarthritis [ID3958]: EAG final cost comparison report (updated following company factual accuracy check and confidential information check)

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AE	adverse event
AESI	adverse events of special interest
AS	ankylosing spondylitis
ASAS	Assessment in SpondyloArthritis
ASQoL	ankylosing spondylitis quality of life
BASDAI	Bath Ankylosing Spondyloarthritis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
bDMARDs	biologic disease modifying anti-rheumatic drugs
CFB	change from baseline
CRP	C-reactive protein
CS	company submission
EAG	External Assessment Group
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
FE	fixed effects
HI	Health index
HLA-B27	human leukocyte antigen B27
HRQoL	health-related quality of life
hsCRP	high sensitivity C-reactive protein
IBD	inflammatory bowel disease
IL-17A	Interleukin-17A
JAK	Janus kinase
MACE	major adverse cardiac events
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
nr-axSpA	non-radiographic axial spondyloarthritis
NSAID	non-steroidal anti-inflammatory drug
OSI	objective signs of inflammation
PAS	Patient Access Scheme
PCS	Physical Component Summary
Q2W	every two weeks
Q4W	every four weeks
RCT	randomised controlled trial
RE	random effects
SF-36	36-Item Short Form
SLR	systematic literature review
SPARCC	Spondyloarthritis Research Consortium of Canada
TNFα	tumour necrosis factor-alpha
VAS	Visual Acuity Score

1 SUMMARY OF THE EAG VIEW OF THE COMPANY'S COST COMPARISON CASE

The remit of the External Assessment Group (EAG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the cost comparison process. Clinical and economic evidence has been submitted to NICE by the company (AbbVie) in support of the use of upadacitinib as a treatment option for patients with non-radiographic axial spondyloarthritis (nr-axSpA). This summary provides a brief overview of the key issues identified by the EAG as being potentially important for decision making.

1.1 Pharmacological, biological, and/or pharmacokinetic differences

Upadacitinib differs to the comparators, ixekizumab and secukinumab, in both route of administration and mechanism of action. Upadacitinib is a Janus kinase (JAK) inhibitor administered orally, whereas ixekizumab and secukinumab are interleukin-17A (IL-17A) inhibitors administered by subcutaneous injection.

1.2 Clinical effectiveness evidence

The population specified in the final scope issued by NICE is adults with active nr-axSpA. The company has presented evidence for a narrower population: adults with active nr-axSpA with objective signs of inflammation (OSI) that is not controlled well enough with non-steroidal anti-inflammatory drugs (NSAIDs) and who are not able to tolerate or achieve an adequate response to tumour necrosis factor-alpha (TNFα) inhibitors. Ixekizumab and secukinumab have been recommended by NICE as treatment options for this population.

The EAG agrees with the company that the SELECT-AXIS 2 trial (upadacitinib versus placebo) is a good quality trial that was well designed and well conducted. As placebo is not a relevant comparator, the company conducted Bayesian network meta-analyses (NMAs) to make comparisons of upadacitinib with IL-17A inhibitors and TNFα inhibitors for the following outcomes: Assessment in SpondyloArthritis International Society 40 (ASAS40), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50, BASDAI change from baseline (CFB) and Bath Ankylosing Spondylitis Functional Index (BASFI) CFB. As the NMAs included trials of TNFα inhibitors, the EAG asked the company to carry out NMAs that only included the SELECT-AXIS-2 trial and placebo-controlled trials of ixekizumab (COAST-X) and secukinumab (PREVENT).

Clinical advice to the EAG is that it is unclear whether the populations of the three pivotal trials are representative of NHS patients with nr-axSpA that is not controlled well enough with NSAIDs and who are not able to tolerate or achieve an adequate response to TNFα inhibitors

but that trial results are generalisable to NHS patients. All patients in the COAST-X trial and most patients in the SELECT-AXIS 2 trial (210/313, 67.1%) and in the PREVENT trial (501/555, 90.3%) were biologic-naïve. The inclusion criteria for the SELECT-AXIS 2 and PREVENT trials specified that patients who were biologic-experienced must not previously have had an adequate response to TNFα inhibitors (and also, in the case of the SELECT-AXIS 2 trial, to IL-17A inhibitors). However, clinical advice to the EAG is that there is no reason to assume that a patient who has been treated with a TNFα inhibitor (biologic-experienced) would have a different response to upadacitinib or IL-17A inhibitors compared to a patient who is biologic-naïve. Evidence from trials of IL-17A inhibitors for patients with ankylosing spondylitis (AS) suggests that patients who are biologic-naïve have numerically higher response rates to treatment than patients previously treated with TNFα inhibitors.

As with its original NMAs, the company chose the fixed effects model for all NMAs. NMAs were conducted for ASAS40, BASDAI50, BASDAI CFB and BASFI CFB. NMAs were conducted for the OSI population as the SELECT-AXIS 2, COAST-X and PREVENT trials included patients with OSI only.

The EAG considers that the NMA approach is valid and appropriate, but highlights:

- heterogeneity in terms of baseline characteristics and follow-up for response may be an issue affecting the results
- because there are only three trials and no-head-to-head comparisons of treatments, there is no potential for checking for consistency in the network, even though this is a fundamental assumption
- for the comparison of upadacitinib versus secukinumab, the company presented results for upadacitinib versus secukinumab without a loading dose; NICE only recommends secukinumab with a loading dose
- it is unclear whether the company included all three arms of the COAST-X and PREVENT trials.

However, overall, the EAG consider that the simplified NMAs requested by the EAG are more appropriate for decision making than the more complex NMAs presented in the company submission.

For all NMA outcomes, median values numerically favour upadacitinib versus ixekizumab (except for BASDAI50) and upadacitinib versus secukinumab. However, for the two binary outcomes (ASAS40 and BASDAI50), the credible intervals are wide and include unity for comparisons of upadacitinib versus ixekizumab and upadacitinib versus secukinumab; for the two continuous outcomes (BASDAI CFB and BASFI CFB) the credible intervals are wide and include zero. Therefore, in all these cases, the median values could indicate greater health benefits for upadacitinib, ixekizumab or secukinumab.

The EAG assessed whether upadacitinib, ixekizumab and secukinumab safety profiles were comparable using data from the SELECT-AXIS 2, COAST-X and PREVENT trials. The EAG acknowledges that these comparisons are naïve. As differences in the incidences of adverse events (AEs) between trials are likely to be influenced by differences in trial design, length of follow-up and differences in AE definitions, it is difficult to draw any definitive conclusions. However, overall, the EAG considers that the safety profiles of upadacitinib, ixekizumab and secukinumab are broadly similar. After a minimum of 52 weeks, there were a small number of patients who developed uveitis events in all three trials (SELECT-AXIS 2: 1/156, 1%; COAST-X: 3/198, 1.5%; PREVENT: 9/369, 2.4%). No patients in the SELECT-AXIS 2 trial at week 14 (and, overall, ≤3 patients in each of the COAST-X and PREVENT trials) developed inflammatory bowel disease, venous thromboembolic, major adverse cardiac or malignancy events.

1.3 Cost effectiveness evidence

If the efficacy of upadacitinib is equal to the efficacy of ixekizumab and/or secukinumab, the EAG considers that, when using the Patient Access Scheme (PAS) price for upadacitinib and list prices for ixekizumab and secukinumab, the company cost comparison results provide robust estimates of the likely cost savings, over 5-years, for patients treated with upadacitinib compared to patients treated with ixekizumab or secukinumab.

Upadacitinib, ixekizumab and secukinumab are available to the NHS at confidential PAS prices and the EAG has provided a confidential appendix showing results for the cost comparison of upadacitinib versus ixekizumab and upadacitinib versus secukinumab using confidential prices for upadacitinib, ixekizumab and secukinumab.

The EAG considers that there are no critical issues relating to the economic evidence/model submitted by the company and has not generated any alternative cost comparison results.

1.4 EAG conclusions

The EAG considers that the company has not provided sufficient evidence to support the conclusion that upadacitinib is similar to ixekizumab or secukinumab as an absence of evidence is not the same as evidence of absence. The true effect of upadacitinib versus ixekizumab and upadacitinib versus secukinumab could lie anywhere within the 95% credible intervals and this range of values includes values that could indicate clinically important effects in both directions. Therefore, the EAG considers that the clinical effectiveness evidence presented by the company does not support the assumption that treatment with upadacitinib is sufficiently similar to ixekizumab and/or secukinumab to ignore any potential differences in clinical outcomes.

2 INTRODUCTION

Axial spondyloarthritis is a spectrum of diseases that can be classified into two subtypes:[1]

- ankylosing spondylitis (AS), where there is objective signs of inflammation (OSI) from x-ray, also known as radiographic axial spondyloarthritis (rad-axSpA)
- non-radiographic axial spondyloarthritis (nr-axSpA) where inflammation is identified by other OSI, such as elevated levels of C-reactive protein (CRP) and/or via magnetic resonance imaging (MRI).

This appraisal focuses on upadacitinib as a treatment option for active nr-axSpA. The company has chosen to compare the effectiveness of upadacitinib versus two biologic disease modifying anti-rheumatic drugs (bDMARDs), ixekizumab and secukinumab.

This report includes the External Assessment Group (EAG) view on whether it is appropriate to appraise this topic via the National Institute for Health and Care Excellence (NICE) Cost Comparison Appraisal process. In this EAG report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission. Additional evidence was provided by the company at the clarification stage.

2.1 Pharmacological, biological and pharmacokinetic comparison of upadacitinib, ixekizumab and secukinumab

As shown in Table 1, upadacitinib is a Janus kinase (JAK) inhibitor which differs to ixekizumab and secukinumab in several ways. The company considers (CS, p16 and pp18-19) that upadacitinib addresses an unmet need due to being in oral form and having a mode of action that differs from the interleukin-17A (IL-17A) inhibitors (and also the tumour necrosis factor-alpha [TNFα] inhibitors). If recommended by NICE, upadacitinib would enable patients to receive treatment where alternatives are unsuitable because of patient choice, comorbidities and/or adverse events (AEs). For example, the company highlights:

- the administration route is the third most important consideration (after symptom improvement and cost) when selecting treatment; it has been reported that 49.9% (198/397) of patients with axial spondyloarthritis prefer an oral treatment[2]
- compared to ixekizumab and secukinumab, upadacitinib has a short half-life and may therefore be more suitable for treating patients with recurring infections, or a history of severe infections[3]
- approximately 7% of all patients with nr-axSpA experience inflammatory bowel disease (IBD), which renders treatment with IL-17A inhibitors unsuitable.[4]

Table 1 Comparison of key features: upadacitinib, ixekizumab and secukinumab

Feature	Upadacitinib	Ixekizumab	Secukinumab
Method of administration	Oral	Injection	Injection
Class of drug	JAK inhibitor	IL-17A inhibitor	IL-17A inhibitor
Mechanism of action	Selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3. JAKs are intracellular enzymes involved in a broad range of cellular processes including inflammatory responses, haematopoiesis and immune surveillance. JAK1 is important in inflammatory cytokine signals	IgG4 monoclonal antibody that binds with high affinity (<3pM) and specificity to IL-17A (both IL-17A and IL-17A/F). Elevated concentrations of IL-17A promote inflammation leading to erosive bone damage and pathological new bone formation	Fully human IgG1/κ monoclonal antibody that selectively binds to IL-17A. Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17A receptor to prevent the release of proinflammatory cytokines, chemokines and mediators of tissue damage
Half-life	8 to 14 hours	13 days	21-22 days

IG= Immunoglobulin; IL-17A=interleukin-17A; JAK=Janus kinase; nr-axSpA=non-radiographic axial spondyloarthritis
Source: CS, Table 2, Summary of Product Characteristics documents[5-7] and DRUGBANK Online[8-10]

2.2 Marketing authorisations and NICE recommendations for upadacitinib, ixekizumab and secukinumab

The marketing authorisations[5-7] of upadacitinib, ixekizumab and secukinumab are presented in Table 2. The marketing authorisations[5-7] for treating nr-axSpA (and AS) are similar. NICE recommendations[11-13] for treating nr-axSpA (and AS) are presented in Table 3.

Table 2 Comparison of marketing authorisations: upadacitinib, ixekizumab and secukinumab

Feature	Upadacitinib	Ixekizumab	Secukinumab
Brand name	Rinvoq™	Taltz®	Cosentyx®
Marketing authorisation (nr-axSpA)	Indicated for the treatment of active nr-axSpA in adult patients with OSI as indicated by elevated CRP and/or MRI, who have responded inadequately to NSAIDs	Indicated for the treatment of adult patients with active nr-axSpA with OSI as indicated by elevated CRP and/or MRI who have responded inadequately to NSAIDs	Indicated for the treatment of active nr-axSpA with OSI as indicated by elevated CRP and/or MRI evidence in adults who have responded inadequately to NSAIDs
Marketing authorisation (AS)	Indicated for the treatment of adult patients with active AS who have responded inadequately to conventional therapy	Indicated for the treatment of adult patients with active AS who have responded inadequately to conventional therapy	Indicated for the treatment of adult patients with active AS who have responded inadequately to conventional therapy
Dose schedule (nr-axSpA and AS)	15mg prolonged-release tablet once daily with or without food which may be taken at any time of day	160mg (two 80mg injections) by subcutaneous injection at Week 0, followed by 80mg every 4 weeks	150mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing*
Other disease areas indicated for	Rheumatoid arthritis Psoriatic arthritis Atopic dermatitis Ulcerative colitis	Adult plaque psoriasis Paediatric plaque psoriasis Psoriatic arthritis	Adult plaque psoriasis Paediatric plaque psoriasis Psoriatic arthritis

* For AS, based on clinical response, the dose can be increased to 300mg, given as one subcutaneous injection or as two subcutaneous injections of 150mg

AS=ankylosing spondylitis; CRP=C-reactive protein; IL-17A=interleukin 17A; JAK=Janus Kinase; nr-axSpA=non-radiographic axial spondyloarthritis; MRI=magnetic resonance imaging; nr-axSpA=non-radiographic spondyloarthritis; NSAID=nonsteroidal anti-inflammatory drug; OSI=objective signs of inflammation

Source: CS, Table 2, Summary of Product Characteristics documents[5-7] and updated information provided by the company following company factual accuracy check and confidential information check

Table 3 Comparison of NICE recommendations for nr-axSpA and AS: upadacitinib, ixekizumab and secukinumab

Disease area	Upadacitinib	Ixekizumab	Secukinumab
nr-axSpA	ID3958: The company are seeking a similar recommendation as ixekizumab and secukinumab for treating active nr-axSpA	TA718: Recommended as an option for treating active nr-axSpA with OSI (shown by elevated CRP or MRI) that is not controlled well enough with NSAIDs, in adults. It is recommended only if TNFα inhibitors are not suitable or do not control the condition well enough, and the company provides ixekizumab according to the commercial arrangement	TA719: Recommended as an option for treating active nr-axSpA with OSI (shown by elevated CRP or MRI) that is not controlled well enough with NSAIDs, in adults. It is recommended only if TNFα inhibitors are not suitable or do not control the condition well enough, and the company provides ixekizumab according to the commercial arrangement
AS	ID3848 (FAD): Recommended as an option for treating active ankylosing spondylitis that is not controlled well enough with conventional therapy in adults, only if: TNFα inhibitors are not suitable or do not control the condition well enough, and the company provides upadacitinib according to the commercial arrangement	TA718: Recommended as an option for treating active AS that is not controlled well enough with conventional therapy, or active nr-axSpA with OSI (shown by elevated CRP or MRI) that is not controlled well enough with NSAIDs, in adults. It is recommended only if: TNFα inhibitors are not suitable or do not control the condition well enough, and the company provides ixekizumab according to the commercial arrangement	TA407: Recommended, within its marketing authorisation, as an option for treating active AS in adults whose disease has responded inadequately to conventional therapy (NSAIDs or TNFα inhibitors). The drug is recommended only if the company provides it with the discount agreed in the patient access scheme

AS=ankylosing spondylitis; CRP=C-reactive protein; FAD=Final Appraisal Document; IL-17A=interleukin 17A; JAK=Janus Kinase; nr-axSpA=non-radiographic axial spondyloarthritis; MRI=magnetic resonance imaging; nr-axSpA=non-radiographic spondyloarthritis; NSAID=nonsteroidal anti-inflammatory drug; OSI=objective signs of inflammation; TNFα=tumour necrosis factor-alpha

Source: NICE webpages[1,11-14] (updated following company factual accuracy check and confidential information check)

2.3 Main sources of clinical effectiveness evidence for the intervention and comparators

The main source of clinical effectiveness evidence for the intervention (upadacitinib) is the ongoing SELECT-AXIS 2 trial (NCT04169373) comparing upadacitinib versus placebo. The protocol for this study includes two standalone studies with randomisation, data collection, analysis and reporting conducted independently:

- Study 1 includes only patients with AS patients (no nr-axSpA patients)
- Study 2 includes only nr-axSpA patients.

Only patients from study 2 with nr-axSpA were reported in the CS and this EAG report and so all references made to SELECT-AXIS 2 trial relate to study 2 only. SELECT-AXIS 2 trial results are yet to be published, however, the company has provided data from the clinical study report.[15] The trial results have since been published in the publication by Deodhar et al 2022.[16]

The main sources of clinical effectiveness data for the comparators (ixekizumab and secukinumab) are the placebo-controlled COAST-X and PREVENT trials, respectively. The COAST-X and PREVENT trials include two arms of ixekizumab and secukinumab:

- ixekizumab 80mg every two weeks (Q2W)
- ixekizumab 80mg every four weeks (Q4W), which is the NICE recommended dose[11]
- secukinumab 150mg Q4W with a loading dose, which is the NICE recommended dose[13]
- secukinumab 150mg Q4W without a loading dose.

The primary publications for these trials are Deodhar et al 2020[17] (COAST-X) and Deodhar et al 2021[18] (PREVENT). Secondary sources for each trial (COAST-X;[19,20] PREVENT[21]) were also used to inform the company network meta-analyses (NMAs).

3 EAG CRITIQUE OF THE COMPANY DECISION PROBLEM

The company has developed a decision problem based on information presented in the final scope[1] issued by NICE. The EAG discusses the extent to which the company decision problem meets the final scope[1] in Section 3.1 to Section 3.6.

3.1 Population

The population specified in the final scope[1] issued by NICE is adults with active nr-axSpA. The company has presented evidence for a narrower population: "Adults with active [nr-axSpA] with [OSI] that is not controlled well enough with non-steroidal anti-inflammatory drug (NSAIDs) and who are not able to tolerate or achieve an adequate response to TNFα inhibitors" (CS, Table 1). This population aligns with the subgroups specified in the final scope[1] issued by NICE. Ixekizumab (TA718[11]) and secukinumab (TA719[13]) are recommended by NICE as treatment options for this population.

The company highlights (CS, p7) that, "The anticipated licence wording for upadacitinib in this indication is for the treatment of active nr-axSpA in adult patients with OSI who have responded inadequately to NSAIDs". Therefore, the population addressed in this appraisal is also narrower than the anticipated licensed population.

3.2 Comparators

The comparators listed in the final scope[1] issued by NICE were IL-17A inhibitors (ixekizumab and secukinumab), TNFα inhibitors (adalimumab, etanercept, certolizumab pegol and golimumab) and established clinical management without biological treatments. Clinical advice to the company was that established clinical management consists of NSAIDs and physiotherapy.

The EAG agrees with the company that IL-17A inhibitors (ixekizumab and secukinumab) are the only relevant comparators for this appraisal. The company and EAG agree that TNFα inhibitors are not relevant comparators as the population addressed by the company is patients with active nr-axSpA with [OSI] that is not controlled well enough with NSAIDs and who are not able to tolerate or achieve an adequate response to TNFα inhibitors. The company and EAG consider that established clinical management without biological treatments is not relevant because the population addressed by the company includes patients whose condition is not controlled well enough with NSAIDs.

There are currently no published data from randomised controlled trials (RCTs) that compare the clinical effectiveness of upadacitinib versus ixekizumab or versus secukinumab as a treatment for patients with nr-axSpA. The comparator in the pivotal SELECT-AXIS 2 trial is placebo. Therefore, the company conducted NMAs to compare the clinical effectiveness of upadacitinib versus ixekizumab and upadacitinib versus secukinumab.

The population addressed by the company was patients with nr-axSpA that is not controlled well enough with NSAIDs and who are not able to tolerate or achieve an adequate response to TNFα inhibitors. The EAG therefore considered that NMAs which only included ixekizumab and secukinumab (linked by placebo since there were no head-to-head comparisons of active treatments) should have been conducted, i.e., NMAs including only the SELECT-AXIS 2, COAST-X and PREVENT trials. The EAG requested that the company conduct these simplified NMAs at the clarification stage.

3.3 Outcomes

The final scope[1] issued by NICE, specified broad outcome measures of disease activity, functional capacity, disease progression, pain, peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis), symptoms of extra-articular manifestations (including uveitis, IBD and psoriasis), AEs and health-related quality of life (HRQoL). The company presented results for endpoints that addressed all the broad outcomes. All outcome measures are based on a patient's subjective experience, except for OSI which is measured by high sensitivity C-reactive protein (hsCRP) or MRI.

The company NMA outcomes were measures of disease activity and functional capacity (CS, Table 3). Disease activity was captured through the Assessment in SpondyloArthritis international Society 40 (ASAS40), Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) and BASDAI change from baseline (CFB). Functional capacity was recorded using the Bath Ankylosing Spondylitis Functional Index (BASFI) CFB. These outcomes are the same outcomes that were used for the NMAs that informed decision making in the NICE appraisals for ixekizumab (TA718[11]) and secukinumab (TA719[13]). The company highlights (CS, p48) that these are also the key clinical outcomes recommended by the British Society of Rheumatology guidelines[22] to assess nr-axSpA activity. Additional NMA outcomes measuring disease activity (ASAS20 and assessment of AS), partial remission [ASAS PR]) and pain (patient's assessment of total back pain CFB) were presented in the CS, Appendix K.

Clinical advice to the EAG is that ASAS40 is an appropriate outcome measure for clinical trials as it is a composite measure comprising patient global disease assessment, spinal pain,

function (BASFI score) and inflammation (using mean score from two questions of the BASDAI). The NICE recommendations for ixekizumab (TA718[11]) and secukinumab (TA719,[13]) specify that in clinical practice, response should be measured by:

- BASDAI: either a reduction in the BASDAI score to 50% of the pre-treatment value (i.e., BASDAI50) or by ≥2 units in BASDAI CFB and
- spinal pain Visual Analogue Scale (VAS): a reduction ≥2cm.

Clinical advice to the EAG is that symptoms of extra-articular manifestations and other AEs should also be considered when deciding whether a patient can tolerate treatment.

3.4 Economic analysis

The company has presented a cost comparison analysis (CS, Section 4.3). The only differences between the three treatments considered in the company cost comparison analysis are acquisition costs and the training cost associated with self-administered injections.

3.5 Subgroups to be considered

It is stated in the final scope[1] issued by NICE that, "If the evidence allows consideration will be given to subgroups who have not received [TNFα] inhibitors, and those for whom [TNFα] inhibitors are not suitable or do not control the condition well enough". These are the patients considered by the company (Section 3.1). The majority of patients included in the trials for which there is evidence were treatment naïve. It is unknown how many patients were not able to tolerate or achieve an adequate response to TNFα inhibitors .

3.6 Other considerations

3.6.1 Equality issues

It is not anticipated that any equality issues will arise if upadacitinib is recommended by NICE. However, the company highlights that during the NICE appraisal of TNFα inhibitors as treatment options for AS and nr-axSpA treatment (TA383),[23] an equality concern arose regarding the use of BASDAI and spinal pain VAS scores for assessing response to treatment. Hence, guidance issued by NICE for TA383[23] states that, "When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate[23]". This recommendation is also repeated in NICE guideline 65[24] (Spondyloarthritis in over 16s: diagnosis and management).

3.6.2 Impact on treatment pathway

Clinical advice to the EAG is that currently secukinumab is used more often than ixekizumab, partly due to it being available as a treatment option in the separate AS indication for longer than ixekizumab. Clinical advice to the EAG is that in NHS clinical practice, it is unusual for a patient to switch from secukinumab to ixekizumab (or vice versa) other than for AEs (such as injection site reactions). Currently, therefore, patients who have stopped responding to an IL-17A inhibitor have limited treatment options.

Clinical advice to the EAG is that ideally, upadacitinib, ixekizumab and secukinumab should all be available as second-line or third-line treatment options. The choice of whether to offer upadacitinib or an IL-17A inhibitor second-line would depend on a number of different factors. These include consideration of whether patients have needle phobia, dexterity issues or underlying health conditions and whether patients are at risk of AEs or experience AEs with IL-17A or JAK inhibitors. For example, clinical advice to the EAG is that:

- the shorter half-life of upadacitinib would enable patients with infections or patients due to have an operation to continue treatment for nr-axSpA when IL-17A inhibitors would be unsuitable due to their longer half-life
- because of post-marketing safety concerns[25] in relation to cardiovascular events and malignancy with another JAK inhibitor (tofacitinib), IL-17A inhibitors would be preferred for patients with a history of, or considered at risk of developing, these conditions
- IL-17A inhibitors may also be preferred for patients with uveitis and psoriasis
- given upadacitinib has received a positive opinion from the European Medicines Agency Committee for Medicinal Products for Human Use for the treatment of ulcerative colitis (a chronic relapsing systemic IBD),[26] upadacitinib may be preferred for patients with a history of IBD.

Clinical advice to the EAG is that, having taken all the above considerations into account, if upadacitinib, ixekizumab and secukinumab were all still viable treatment options, then the key consideration would be cost, with the cheapest treatment option being preferred.

4 SUMMARY OF THE EAG CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE

4.1 Systematic literature review

4.1.1 Searches

The company conducted literature searches to identify RCTs reporting efficacy and safety data for relevant treatments for patients with nr-axSpA in October 2021. Search strategies and outcomes are described in the company systematic literature review (SLR) report (CS, Appendix D). The EAG is satisfied that the company's search strategies were comprehensive and appropriate.

The EAG searches (conducted in May 2022) did not identify any additional relevant studies of upadacitinib, ixekizumab or secukinumab.

4.1.2 Included studies

The company SLR included 12 placebo-controlled RCTs.[15,17,18,27-35] The company presented information about these trials in the CS (Appendix D). Only three trials included a relevant intervention or comparator for this appraisal: the SELECT-AXIS 2, COAST-X and PREVENT trials. The remaining nine trials[27-35] compared TNFα inhibitors with placebo. As the population considered by the company for this appraisal is patients with nr-axSpA that is not controlled well enough with NSAIDs and who are not able to tolerate or achieve an adequate response to TNFα inhibitors, the EAG considers that these nine trials are not relevant to this appraisal.

4.2 Direct clinical effectiveness evidence

The SELECT-AXIS 2 trial provides clinical effectiveness evidence for the comparison of upadacitinib versus placebo. The trial [redacted] UK patients and only included a small proportion of patients from Western Europe ([redacted], [redacted]). Clinical advice to the EAG is that SELECT-AXIS 2 trial results are generalisable to NHS patients.

4.2.1 SELECT-AXIS 2 trial: quality assessment

The company quality assessment of the SELECT-AXIS 2 trial (using the Centre for Reviews and Dissemination quality assessment checklist[36]) is presented in the CS (Table 10). The EAG agrees with the company responses and considers that the SELECT-AXIS 2 trial was well designed and well conducted.

4.2.2 SELECT-AXIS 2 trial: statistical approach

The company describes their statistical approach to analysing the SELECT-AXIS 2 trial data in the CS, the trial statistical analysis plan[15] and the SELECT-AXIS 2 trial protocol.[37] The EAG

considers that appropriate statistical methods were used to analyse SELECT-AXIS 2 trial data (Appendix 1, Section 8.1).

4.2.3 SELECT-AXIS 2 trial: efficacy results

All efficacy outcomes were reported at Week 14. A statistically significant greater proportion of patients treated with upadacitinib (70/156, 44.9%) achieved ASAS40 than patients treated with placebo (35/157, 22.5%) (CS, Table 12). Statistically significant differences favouring upadacitinib versus placebo were reported for 12 of 14 multiplicity-controlled secondary efficacy endpoints (CS, Table 13). The use of multiplicity-controlled endpoints increases confidence that these results did not occur by chance. Upadacitinib also showed an improvement in treatment response for additional endpoints that were not multiplicity-controlled: patient's global assessment of disease activity (a component of ASAS), inflammation (measured by components of BASDAI, hsCRP and MRI spondyloarthritis research consortium of Canada [SPARCC] spine scores) and various measures of pain (CS, Appendix J, Section B.1.3).

4.2.4 SELECT-AXIS 2 trial: subgroup results

Pre-specified subgroup analyses for ASAS40 are presented in the CS (Appendix J, Section B.1.4).

[redacted] The EAG highlights that the trial was not powered specifically to show statistically significant differences for subgroups.

4.3 Company network meta-analyses

In the absence of direct comparisons of the efficacy and safety of upadacitinib versus ixekizumab and upadacitinib versus secukinumab, the company conducted NMAs.

4.3.1 Company approach to NMAs

The company adopted a Bayesian NMA approach (CS, Appendix K, Section 4). The company has presented NMA results for upadacitinib versus ixekizumab, and upadacitinib versus secukinumab (CS, Table 16 to Table 19).

Bayesian NMAs were conducted for the following outcomes:

- ASAS40, BASDAI50, BASDAI CFB and BASFI CFB (CS, main body)
- ASAS20, ASAS PR and patient assessment of total back pain CFB (CS, Appendix K).

The company's analytic approach is described in detail in the CS (Appendix K, Section 4.5) and includes a description of the methods and assumptions employed for:

- data imputation
- feasibility assessment
- model specification
- prior distributions
- model fit and comparison
- consistency
- model outputs and baseline model.

The EAG considers that the analytic approach described, and all assumptions made, were appropriate.

The company chose the fixed effects (FE) model for all NMAs. This choice was largely due to data sparsity which resulted in a lack of convergence of regression coefficients that were not statistically significant with random effects (RE) and risk-adjusted FE and RE models (CS, Appendix K, Section 5.3). Data sparsity also meant the consistency assumption could only be assessed in a subset of outcomes. It is only possible to assess the consistency assumption where a single loop is present in a network. This only occurred as a result of a loop formed by the c-axSpAnd trial[27] and RAPID-axSpA trial[30] which linked certolizumab pegol (400 mg loading dose at weeks 0, 2, 4, then maintenance dose 200 mg Q2W) and placebo for the ASAS40, BASDAI CFB, and BASFI CFB outcomes (CS, Appendix K, Section 5.5).

Overall, the EAG considers that the NMA approach is valid and appropriate. However, the EAG highlights:

- heterogeneity may be an issue affecting the results (see Appendix 2, Section 8.2.3 for detail), particularly by including trials TNFα inhibitors (see Section 4.3.2).
- for the comparison of upadacitinib versus secukinumab, in the main body of the CS (Table 16 to Table 19) the company presented results for upadacitinib versus secukinumab without a loading dose; NICE only recommends secukinumab with a loading dose.[13]

4.3.2 Trials included in the company NMAs

Published data from phase III or phase IV RCTs (or RCTs which did not specify a phase) that were identified by the company SLR (CS, Appendix D) were used in the NMAs. All included RCTs reported, either directly or through imputation:

- the number of patients in each treatment arm who did and did not experience the outcome of interest (binary outcomes: ASAS20, ASAS40, ASASPR, BASDAI50)
- the mean value, standard error (SE), and number of patients assessed for the outcome of interest in each treatment arm (continuous outcomes: BASDAI CFB, BASFI CFB and patient's assessment of total back pain CFB).

The company included data from the following nine placebo-controlled trials (CS, Appendix K): the ABILITY-1,[35] C-axSpAnd,[27] COAST-X,[17] EMBARK,[28] GO-AHEAD,[34] Haibel 2008 (NCT00235105),[29] PREVENT,[18] RAPID-axSpA[30] and SELECT-AXIS 2 trials.

The complete treatment network for the NMAs is presented in the CS (Figure 5). Different bDMARDs were linked only via placebo, although two different doses of ixekizumab, secukinumab and certolizumab pegol were included in three 3-arm trials (COAST-X, PREVENT and RAPID-axSpA[30]).

The EAG considers that since TNFα inhibitors are not considered relevant comparators including results from TNFα inhibitor trials in the NMAs adds unnecessary complexity. Unnecessary trial and patient variation could cause heterogeneity or inconsistency. Hence the EAG requested that the company provide results from NMAs including only data from the SELECT-AXIS 2, COAST-X and PREVENT trials at the clarification stage. The EAG consideration of this evidence is presented below (Section 4.4). For completeness, EAG consideration of the original NMAs is presented in Appendix 2 (Section 8.2).

4.4 Network analyses requested by the EAG

4.4.1 Approach to NMAs requested by the EAG

As requested by the EAG (Clarification Question A7), the company conducted NMAs using a reduced network which only included data from the SELECT-AXIS, COAST-X and PREVENT trials. As with its original NMAs (See Section 4.3.1), the company chose the FE model for all NMAs. NMAs were conducted for ASAS40, BASDAI50, BASDAI CFB and BASFI CFB. NMAs

were conducted for the OSI population as the SELECT-AXIS 2, COAST-X and PREVENT trials included patients with OSI only.

As with the more complex NMAs presented in the CS, the EAG considers that the NMA approach is valid and appropriate, but again highlights heterogeneity may still be an issue affecting the results (see Section 4.4.3). In addition:

- because there are only three trials and no-head-to-head comparisons of treatments, there is no potential for checking for consistency in the network, even though this is a fundamental assumption (see Section 4.4.3)
- for the comparison of upadacitinib versus secukinumab, the company presented results for upadacitinib versus secukinumab without a loading dose; NICE only recommends secukinumab with a loading dose[13]
- it is unclear whether the company included all three arms of the COAST-X and PREVENT trials.

However, overall, the EAG consider that the simplified NMAs requested by the EAG are more appropriate for decision making than the more complex NMAs presented in the CS.

4.4.2 Quality assessment of trials included in NMAs requested by the EAG

The company quality assessments of the trials it included in its NMAs, including the three trials of interest, are presented in Appendix D, Sub-appendix I. The EAG agrees with the company that the three trials are of good quality.

4.4.3 Patient characteristics and assessment of heterogeneity of trials included in the NMAs requested by the EAG

The company assessment of heterogeneity (CS, Section B.3.9.3) identified that the number and proportion of patients who had previously received a bDMARD (biologic-experienced) included in the SELECT-AXIS 2 trial (103/313, 32.9%), the COAST-X trial (0/303) and the PREVENT trial (54/555, 9.7%) were different. However, clinical advice to the EAG is that there is no reason to assume that a patient who has been treated with a TNFα inhibitor (biologic-experienced) would have a different response to upadacitinib or IL-17A inhibitors compared to a patient who is biologic-naïve. Evidence from trials of IL-17A inhibitors[38-41] for patients with AS suggests that patients who are biologic-naïve have numerically higher response rates to treatment than patients previously treated with TNFα inhibitors.

The EAG compared SELECT-AXIS 2, COAST-X and PREVENT trial eligibility criteria (Appendix 3, Section 8.3, Table 13) and patient baseline characteristics (Appendix 3, Section 8.3, Table 14) which had been identified a priori as potential treatment effect modifiers or prognostic factors by the company (CS, p63). The EAG identified the following differences between the trials:

- mean duration from diagnosis and mean duration of symptoms were shorter in the PREVENT trial (2.12 to 2.96 years and 8.39 to 8.72 years, respectively) than in the SELECT-AXIS 2 (4.35 to 4.55 years and 9.00 to 9.20 years, respectively) and COAST-X trials (3.10 to 4.20 years and 10.10 to 11.30 years, respectively. Clinical advice to the EAG is that patients with a shorter duration of disease may have a better response to treatment than those with a longer duration
- mean CRP level was lower in the SELECT-AXIS 2 trial ([redacted]mg/L to [redacted]mg/L) than in the COAST-X (12.10mg/L to 14.30mg/L) and PREVENT trials (9.67mg/L to 13.17mg/L). Clinical advice to the EAG is that patients with higher CRP levels may have a better response to treatment than those with lower levels. However, the three trials used the same threshold (>5mg/L) to define elevated CRP level and the proportion of patients who had elevated CRP levels was similar between trials
- the proportion of patients who were human leukocyte antigen B27 (HLA-B27) positive was lower in the SELECT-AXIS 2 trial (183/313, 58.5%) than in the COAST-X (221/303, 72.9%) and PREVENT trials (382/555, 68.8%). Clinical advice to the EAG is that HLA-B27 is a marker of disease severity
- the proportion of patients who showed sacroiliac joint inflammation on MRI was lower in the SELECT-AXIS 2 trial (136/313, 43.5%) than in the COAST-X (217/303, 71.6%) and PREVENT trials (405/555, 73.0%). Clinical advice to the EAG is that joint inflammation on MRI is a marker of disease severity
- the proportion of patients who received concomitant NSAIDs was lower in the SELECT-AXIS 2 trial (234/313, 74.8%) than in the COAST-X (272/303, 89.8%) and PREVENT trials (463/555, 83.4%). Clinical advice to the EAG is that NSAID use can lower the inflammatory markers and reduce MRI scan signal of inflammation.

In addition to differences in baseline characteristics, outcomes were measured at different timepoints across the trials (varied from 14 weeks in the SELECT-AXIS 2 trial to 16 weeks for the trials of ixekizumab and secukinumab). The EAG considers that these areas of heterogeneity may impact treatment outcomes and therefore may cast doubt on the validity of the NMA transitivity assumption. To test whether these differences result in statistical heterogeneity and impact on the results would require the conduct of subgroup, sensitivity or meta-regression analyses. However, to conduct these analyses would require data from multiple studies that make each treatment comparison directly. The EAG acknowledges that there are no relevant head-to-head studies that make such analyses possible.

4.4.4 NMA inputs: individual trial results

The NMA inputs from the SELECT-AXIS 2, COAST-X and PREVENT trials are presented in Appendix 4, Section 8.4, Table 15. Although the company did not present SELECT-AXIS 2 trial results for the BASDAI CFB outcome for the SELECT-AXIS 2 trial in the CS, the data was available and extracted from the CSR (Table 14.2 26) for inputting into the NMAs.

4.4.5 Results from the NMAs requested by the EAG

The results provided relative effect estimates (odds ratios and mean differences) and credible intervals for upadacitinib versus placebo, ixekizumab and secukinumab (Clarification Question A7, Table 6 to Table 9).

For the comparison of upadacitinib versus placebo, the results show that the credible intervals exclude the point of no effect (unity) for the binary outcomes ASAS40 and BASDAI50 and exclude the point of no effect (zero) for the continuous outcomes BASDAI CFB and BASFI CFB (Table 4). Therefore, these results suggest statistical significance in favour of upadacitinib versus placebo. However, placebo is not a relevant comparator for this appraisal.

For the comparison of upadacitinib versus relevant comparators, median values numerically favour upadacitinib versus ixekizumab (except for BASDAI50) and upadacitinib versus secukinumab (Table 4). However, the credible intervals are wide and include unity for comparisons of upadacitinib versus ixekizumab and upadacitinib versus secukinumab for the two binary outcomes (ASAS40 and BASDAI50) and include zero for the two continuous outcomes (BASDAI CFB and BASFI CFB). Therefore, the health benefits for upadacitinib, ixekizumab or secukinumab could be similar, but there could also be greater health benefits for upadacitinib, ixekizumab or secukinumab.

Overall, the results were very similar to those from the company NMAs which included all nine placebo-controlled trials, as presented in the CS (CS, Table 16 to Table 19). Therefore, while the results are presented for upadacitinib versus the incorrect dose of secukinumab (no loading dose), it is likely that the results for upadacitinib versus the correct dose of secukinumab (with loading dose) would be similar to those presented in Appendix 2 (Section 8.2.4, Table 11 and Table 12).

Table 4 Results from NMAs requested by the EAG: comparator versus upadacitinib, median (95% credible interval)

Outcome	Placebo	IXE Q4W	SEC (no LD)
ASAS40 (OR)[a]	[redacted]	[redacted]	[redacted]
BASDAI50 (OR)[a]	[redacted]	[redacted]	[redacted]
BASDAI CFB (MD)[b]	[redacted]	[redacted]	[redacted]
BASFI CFB (MD)[b]	[redacted]	[redacted]	[redacted]

[a] OR>1.00, result favours upadacitinib
[b] Mean difference<0.00, results favour upadacitinib
ASAS40=assessment of ankylosing spondylitis 40; BASDAI50=Bath ankylosing spondylitis disease activity index 50, BASFI=Bath ankylosing spondylitis functional index; CFB=change from baseline; IXE80 Q4W=ixekizumab 80mg every 4 weeks; MD=mean difference; OR=odds ratio; SEC150 (No LD)=secukinumab 150mg with no loading dose
Source: Company response to Clarification Question A7, Table 6 to Table 9

4.5 Health-related quality of life

The company did not present any comparison of HRQoL data for upadacitinib versus ixekizumab or upadacitinib versus secukinumab.

Measures of HRQoL reported in the CSR for the SELECT-AXIS 2 trial included results from the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) Health State Instrument and 36-Item Short Form (SF-36) Health Survey Physical Component Summary (PCS). These results were not reported in the CS. [redacted]. Two of the SELECT-AXIS 2 trial secondary endpoints (AS quality of life [ASQoL] CFB and ASAS Health index [HI] CFB) presented in the CS were measures of HRQoL specific to AS. At Week 14, patients treated with upadacitinib achieved a statistically significant greater improvement from baseline in ASQoL and ASAS HI than patients treated with placebo (CS, Table 13).

While EQ-5D-5L data were reported in the committee papers for the appraisals of ixekizumab[11] and secukinumab,[13] these were redacted. At Week 16 in the COAST-X trial, patients in the ixekizumab arms achieved a statistically significant greater improvement from baseline in SF-36 PCS than patients treated with placebo. The COAST-X trial did not report ASQoL or ASAS HI CFB data. The PREVENT trial did not report ASAS HI CFB data but reported that at Week 16, patients in the secukinumab arms achieved a statistically significant greater improvement from baseline in ASQoL than patients treated with placebo. SF-36 PCS data from the PREVENT trial were presented at American College of Rheumatology Convergence 2020 conference.[21] At Week 16, patients in the secukinumab arms achieved a statistically significant greater improvement from baseline in SF-36 PCS than patients treated with placebo.

4.6 Safety and tolerability results

The company has presented a summary of SELECT-AXIS 2, COAST-X and PREVENT trial safety outcome results (CS, Table 22). The company did not perform any NMAs to assess the comparative safety and tolerability of upadacitinib versus ixekizumab or upadacitinib versus secukinumab.

The EAG assessed whether the AE profiles of upadacitinib, ixekizumab and secukinumab were comparable using data from the SELECT-AXIS 2, COAST-X and PREVENT trials (Table 5). The EAG acknowledges that the comparisons made in this section are naïve. Differences in the incidence of AEs between trials are likely to be influenced by differences in trial design, length of follow-up and differences in AE definitions. It is therefore difficult to draw any

definitive conclusions about differences and similarities between treatments from the available data.

A smaller proportion of patients reported any AE by Week 14 in the SELECT-AXIS 2 trial (147/313, 47.0%) than by Week 16 in the COAST-X trial (123/200, 61.5%) and Week 20 in the PREVENT trial (327/555, 58.9%) (CS, Table 22). However, the proportion of patients reporting any AE by Week 14 was similar between the upadacitinib (75/156, 48.1%) and placebo arms (72/157, 45.9%). The proportion of patients experiencing serious AEs or treatment discontinuation due to AEs was similar between trials (CS, Table 22). There were [redacted] deaths in the three trials. However, nasopharyngitis appears to be [redacted] for patients treated with upadacitinib ([redacted], [redacted]) than for patients treated with ixekizumab (18/96, 18.8%) or secukinumab (27/185, 14.6%). Clinical advice to the EAG is that nasopharyngitis can be a problem for patients treated with IL-17A inhibitors in clinical practice.

Table 5 Adverse events reported in ≥5% participants in one or more of the trial arms in the SELECT-AXIS 2, COAST-X and PREVENT trials

	SELECT-AXIS 2		COAST-X			PREVENT		
	PBO (n=157)	UPA (n=156)	PBO (n=104)	IXE Q2W (n=102)	IXE Q4W (n=96)	PBO (n=186)	SEC (n=185)	SEC (no LD) (n=184)
Length of follow-up	Week 14		Week 52			Up to Week 20		
Any TEAE, n (%)	72 (45.9)	75 (48.1)	60 (57.7)	79 (77.5)	63 (65.6)	101 (54.3)	119 (64.3)	107 (58.2)
Nasopharyngitis, n (%)	[redacted]	[redacted]	8 (7.7)	16 (15.7)	18 (18.8)	23 (12.4)	27 (14.6)	19 (10.3)
Injection site reaction, n (%)	[redacted]	[redacted]	4 (3.8)	17 (16.7)	11 (11.5)	--	--	--
Headache, n (%)	[redacted]	[redacted]	4 (3.8)	5 (4.9)	7 (7.3)	7 (3.8)	17 (9.2)	5 (2.7)
Upper respiratory tract infection, n (%)	[redacted]	[redacted]	4 (3.8)	6 (5.9)	4 (4.2)	7 (3.8)	11 (5.9)	11 (6.0)
Hypertension, n (%)	[redacted]	[redacted]	4 (3.8)	4 (3.9)	6 (6.3)	--	--	--
Diarrhoea, n (%)	[redacted]	[redacted]	--	--	--	7 (3.8)	14 (7.6)	9 (4.9)
Neutropenia, n (%)	[redacted]	[redacted]	9 (8.7)	13 (12.7)	12 (12.5)	--	--	--
IBD, n (%)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.5)
Uveitis, n (%)	0 (0.0)	1 (0.6)	2 (1.9)	2 (1.0)	1 (1.0)	1 (0.5)	2 (1.1)	0 (0.0)

*Different thresholds were used for reporting AE data in the trials as follows: TEAEs>2% patients treated with PBO or UPA in the SELECT-AXIS 2 trial, TEAEs≥5% patients treated with IXE (Q2W and Q4W combined) in the COAST-X trial, AEs>5% patients treated with SEC in the PREVENT trial. Hence '--' denotes where data was not reported, presumably because the threshold was not met in the trial (which could mean there were fewer or no events)
AE= adverse event; IBD=inflammatory bowel disease; IXE=ixekizumab; LD=loading dose; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SE=standard error; SEC=secukinumab; TEAE=treatment-emergent adverse event; UPA=upadacitinib
Source: CS, Table 21, Deodhar 2020[17] and Deodhar 2021[18]

As shown in Appendix 3, Section 8.3, Table 13, patients with active extra-articular manifestations were excluded from the SELECT-AXIS 2, COAST-X and PREVENT trials, although how active extra-manifestations were defined differed across the trials. Clinical advice to the EAG is that in NHS clinical practice, ixekizumab and secukinumab can exacerbate symptoms of extra-articular manifestations. By Week 52:

- there were [redacted] new onset or exacerbations of IBD in the upadacitinib (or placebo) arm up in the SELECT-AXIS 2 trial (CS, p68) whereas in the COAST-X trial, one patient (1/198, 0.5%) in the ixekizumab arms experienced IBD-related events and in the PREVENT trial, 7/369 patients (1.9%) in the secukinumab arms reported IBD-related events
- in the SELECT-AXIS 2 trial, uveitis was reported by [redacted] patients ([redacted]) in the upadacitinib arm, [redacted]; uveitis was experienced by 3/198 (1.5%) patients in the ixekizumab arms of the COAST-X trial (all reported by patients who had prior history of uveitis) and 9/369 (2.4%) patients in the PREVENT trial.

Clinical advice to the EAG is that cardiovascular events and malignancies are adverse events of special interest (AESI):

- in the SELECT-AXIS 2 trial, by Week 52 there were [redacted] venous thromboembolic events (VTE), major adverse cardiac events (MACE) or malignancies
- in the COAST-X trial by 52 weeks, that was one cerebrovascular event (1/102, 1.0%) in the ixekizumab Q2W arm. There were no malignancies
- in the PREVENT trial after a minimum of 52 weeks, there were no MACE in the secukinumab arms; however, three patients randomised to the placebo arm who switched to open-label secukinumab developed malignancies.

The EAG considers that overall, the safety profiles of upadacitinib, ixekizumab and secukinumab are broadly similar. The number of events for symptoms of extra-articular manifestations (IBD and uveitis) and AESIs were small in all three trials but were [redacted] in the SELECT-AXIS 2 trial than in the COAST-X or PREVENT trials. Clinical advice to the EAG is that these trials were not powered to detect AESIs. Further, there are post-marketing safety concerns[25] with another JAK inhibitor, tofacitinib, in relation to cardiovascular events and malignancy. Clinical advice to the EAG is that IL-17A inhibitors would be preferred (rather than a JAK inhibitor) for patients with a history of, or considered at risk of developing, these conditions.

4.7 Additional evidence requested by the EAG

During the clarification process, the EAG requested that the company provide any additional information to support the claim that upadacitinib has similar or greater health benefits than ixekizumab and/or secukinumab (Clarification Question A1). In response, the company:

- reiterated that the results from the NMAs showed no statistically significant differences between upadacitinib and ixekizumab or upadacitinib and secukinumab but that

numerical differences favour upadacitinib (except for BASDAI50 which favours ixekizumab versus upadacitinib)

- highlighted that NICE previously concluded that TNFα inhibitors had similar effectiveness for AS and nr-axSpA based on there being no statistically significant differences between TNFα inhibitors in TA383[23]
- stated that clinical advice to the company is that upadacitinib has comparable health benefits to ixekizumab and secukinumab.

The EAG considers that the company has not provided sufficient justification to conclude that upadacitinib is similar to ixekizumab or secukinumab as an absence of evidence is not the same as evidence of absence.[42] The true effect of upadacitinib versus ixekizumab and upadacitinib versus secukinumab could lie anywhere within the 95% credible intervals and could indicate clinically important effects in both directions.

However, clinical advice to the EAG is that there may be patients who are currently unsuitable for treatment with IL-17A inhibitors who could benefit from treatment with upadacitinib. These include: patients with needle phobia or dexterity issues, patients who have an inadequate response with IL-17A inhibitors and patients at higher risk of IBD or recurrent infections.

5 SUMMARY OF THE EAG CRITIQUE OF COST EFFECTIVENESS EVIDENCE

5.1 Company cost comparison

The company considers that treatment with upadacitinib, ixekizumab and secukinumab generate similar health benefits for patients with nr-axSpA. The company has, therefore, carried out a cost comparison analysis.

5.1.1 Summary of costs and assumptions

The company cost comparison analysis considered upadacitinib, ixekizumab and secukinumab. The key inputs and assumptions in the company cost comparison base case and scenario analyses are shown in Table 6 and Table 7 respectively. The company has assumed that AEs can be ignored in the cost comparison analysis as the company considers that AE rates are similar for upadacitinib, ixekizumab and secukinumab. Whilst monitoring costs are included in the analysis, these are identical for upadacitinib, ixekizumab and secukinumab. Excluding drug costs, the only difference between treatments is that, for patients treated with ixekizumab or secukinumab, there is a one-hour nurse consultation before the first administration to instruct the patient on use of self-injectable treatments.

Table 6 Company cost comparison analysis: key inputs

Input name	Base case value	Source
Upadacitinib cost (every 28 days, PAS price)	[redacted]	AbbVie
Ixekizumab (initial dose, list price)	£2,250.00	BNF[43]
Ixekizumab (maintenance period, every 28 days, list price)	£1,125.00	BNF[43]
Secukinumab (first 28 days, list price)	£3,046.95	BNF[44]
Secukinumab (maintenance period, every 28 days, list price)	£609.39	BNF[44]
Cost of training of self-administration of ixekizumab and secukinumab (one hour Band 6 Nurse)	£48.00	PSSRU 2020[45]

BNF=British National Formulary; PAS=Patient Access Scheme; PSSRU=Personal Social Services Research Unit;
Source: CS, Table 23 and Table 24

Table 7 Company cost comparison analysis: key assumptions

Assumption	Rationale for assumption	Relevant scenario analysis
Time horizon of the analysis is 5 years	This is long enough to capture all treatment-related costs	Time horizon of 1 year and 10 years
Adverse events are not included in the model	Safety profile suggests few serious adverse events for upadacitinib and similar rates of events for upadacitinib, ixekizumab and secukinumab	None undertaken
Monitoring costs are the same for all treatments	Clinical feedback and previous NICE appraisals	None undertaken
Annual discontinuation rate of 6% for all treatments	This rate is consistent with the approach taken in recent NICE technology appraisals for nr-axSpA and considered appropriate by ERG in NICE (TA383[23] and TA719[13]) and by clinical experts whose opinion was sought during interviews (CS, Section B.4.2.6)	Annual discontinuation rate of 11%
Training for one hour is required for ixekizumab and secukinumab injections	Required as treatments are self-administered injections	Removal of training costs

ERG=Evidence Review Group
Source: CS, Section B.4.2

5.1.2 Company cost comparison analysis results

The company base case results are shown in Table 8. Using the PAS price for upadacitinib and the list prices for ixekizumab and secukinumab, the company estimated treatment over 5 years with upadacitinib would cost [redacted] less than treatment with ixekizumab and would cost [redacted] less than treatment with secukinumab.

Table 8 Company base case results (total per person costs over a 5-year time horizon, PAS price for upadacitinib, 6% discontinuation rate, training costs)

Treatment	Upadacitinib	Ixekizumab	Secukinumab
Acquisition	[redacted]	£67,382	£36,245
Administration	-	£48	£48
Total cost	[redacted]	£67,430	£36,293
Incremental cost (upadacitinib versus comparator) PAS price versus list price	-	[redacted]	[redacted]

PAS=Patient Access Scheme
Source: CS, Table 26 and Table 29

The company presents three scenario analyses in the CS (Table 27 to Table 29):

- time horizons from 1-10 years, 6% discontinuation rate and training costs
- 5-year time horizon,11% discontinuation rate and training costs
- 5-year time horizon, 6% discontinuation rate and no training costs.

Treatment with upadacitinib was cost-saving versus ixekizumab, and versus secukinumab in all three scenarios.

5.2 EAG critique of company cost comparison

If the NICE Appraisal Committee considers that upadacitinib, ixekizumab and secukinumab are equivalent/similar then any differences in patient outcomes and AEs can be ignored for decision making purposes. If this is the case, then the EAG considers that, when using the PAS price for upadacitinib and list prices for ixekizumab and secukinumab, the company cost comparison results provide robust estimates of the likely cost savings, over 5-years, for patients treated with upadacitinib compared to patients treated with ixekizumab or secukinumab.

5.3 EAG cost comparison results

As the EAG is satisfied with the company cost comparison analysis methods, the EAG has not generated alternative cost comparison results. Cost effectiveness results using PAS prices for all drugs are presented in a confidential appendix.

6 SUMMARY OF EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

6.1 Submitted clinical effectiveness data

Clinical effectiveness evidence is derived from NMAs. The EAG considers heterogeneity may impact treatment outcomes and therefore may cast doubt on the validity of the NMA transitivity assumption. Nonetheless, the NMAs show that upadacitinib is not statistically significantly superior to ixekizumab and/or secukinumab for the efficacy outcomes presented. Therefore, it is unclear if the outcomes reported in the CS are similar, greater or worse for patients treated with upadacitinib than for patients treated with ixekizumab or secukinumab.

Only a naïve comparison of safety data is possible. This comparison is likely to be influenced by differences in trial design, length of follow-up and in AE definitions. It is, therefore, difficult to draw any definitive conclusions about differences and similarities in AEs between treatments from the available safety data.

6.2 Submitted economic data

When using the PAS price for upadacitinib and list prices for ixekizumab and secukinumab, the company cost comparison provides robust estimates of the likely cost savings over 5-years for patients treated with upadacitinib compared to patients treated with ixekizumab or secukinumab. However, a cost comparison analysis is only appropriate where similar or greater health benefits for the intervention versus comparators can be demonstrated.

6.3 EAG concluding remarks

The EAG considers that the clinical effectiveness evidence presented by the company does not support the assumption that treatment with upadacitinib is sufficiently similar to ixekizumab and/or secukinumab to ignore any potential differences in clinical outcomes.

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8 APPENDICES

8.1 Appendix 1 EAG assessment of statistical approach used in the SELECT AXIS-2 trial

The EAG assessment of the statistical approach used to analyse data from the SELECT AXIS-2 trial is summarised in Table 9.

Table 9 EAG assessment of the statistical approach used to analyse data from the SELECT AXIS-2 trial

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	The analysis populations are reported in the CS (Table 9), CSR[15] (Section 10.3), protocol[37] (Section 7.2) and SAP[15] (Section 4.0): • the FAS population is the same as the ITT population • the per protocol population represents consists of all FAS subjects who did not have any major protocol violations that impact primary efficacy analysis • the safety population includes patients assigned according the treatment actually received. The EAG is satisfied that these analysis populations were clearly defined and pre-specified
Was an appropriate sample size calculation pre-specified?	Yes	Information regarding the estimated sample size is reported in the CS (Table 9), CSR (Section 9.5), protocol (Section 7.7) and SAP (Section 2.4). The EAG is satisfied that the sample size calculation is appropriate and was pre-specified in the SAP included in the CSR
Were all protocol amendments made prior to analysis?	No	Protocol amendments are reported in the CSR (Section 9.6) and protocol (Appendix E) and included: • addition of the Remission-Withdrawal Period at Week 104 • modifications due to the COVID-19 pandemic • update of the statistical methods for handling of missing data. The EAG is satisfied with the rationale for all amendments
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	Information regarding the outcomes evaluated is reported in the CS (Table 7), CSR (Section 9.3), protocol (Section 3.2 and 3.3) and SAP (Section 9.3). The EAG is satisfied that the primary and secondary efficacy outcome definitions and analysis approaches were pre-defined and that the analysis approaches appropriate. Not all outcomes were reported in the CS but were reported in the CSR. The outcomes that were reported in the CS were appropriate for this appraisal
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Information regarding the outcomes evaluated is reported in the CS (Table 7), CSR (Section 9.3), protocol (Section 3.6) and SAP (Section 3.4 and Section 9.0). These included TEAEs, SAEs, AESIs, AEs leading to discontinuation, vital signs, laboratory tests, and physical examination findings. The EAG is satisfied that the analysis approach for AEs was pre-specified and that the analysis approaches are appropriate.
Was a suitable approach employed for handling missing data?	Yes	It is stated in the CS, Section B.3.4.1 (Table 9) that Rubin's method was used to combine the results from the multiple datasets. Further information was provided by the company during the clarification response (Clarification Question A3). The EAG considers the approach taken by the company was appropriate
Were all subgroup and sensitivity analyses pre-specified?	Yes	For the primary outcome (ASAS40) only, the following subgroup analyses are presented in the CS (Appendix J, Section B.1.4): age (<40 and ≥40 years), gender (male and female), BMI (<25 and ≥25), race, geographic regions, hsCRP level at screening, prior bDMARD exposure, MRI (sacroiliac joints) inflammation at screening, hsCRP/MRI sacroiliac joint inflammation at screening, duration since nr-axSpA symptoms and duration since nr-axSpA diagnosis. Subgroup analyses were not presented for any other outcome. The EAG is satisfied that the subgroup analyses were pre-specified in the protocol (Section 7.3) and SAP (Section 8.6)Sensitivity analyses were prespecified in the CSR (Section 8.3.4), protocol (pp57-58) and SAP (Sections 8.3 to 8.5)

AE=adverse event; AESI=adverse event of special interest; ANOVA=analysis of variance; ASAS40=assessment of ankylosing spondylitis 40; bDMARDs=biologic disease modifying anti-rheumatic drugs; BMI=body mass index; CSR=clinical study report; FAS=full analysis set; hsCRP=high sensitivity C-reactive protein; ITT=intention to treat; MRI=magnetic resonance imaging; nr-axSpA=non-radiographic spondyloarthritis; SAE=serious adverse event; SAP=trial statistical analysis plan; TEAE=treatment-emergent adverse event

8.2 Appendix 2 EAG consideration of the NMAs presented in the CS

8.2.1 EAG assessment of statistical approach used for NMAs

The EAG assessment of the statistical approach used for the NMAs is summarised in Table 10.

Table 10 EAG summary and critique of the NMA statistical approaches used by the company

Item	EAG assessment	Statistical approach with EAG comments
Were NMAs conducted for all relevant outcomes?	Yes	The company presents NMAs for outcomes that have been used in previous appraisals (TA 718[11] and TA719[13]). No indirect evidence is presented for AEs or HRQoL which although not presented in TA718[11] and TA719[13] the EAG consider may have provided additional evidence of health benefits
Were the networks of comparators appropriate?	No	The EAG considers that the company networks for the NMAs are appropriate for the population/comparators in the final scope issued by NICE but not the population/comparators in the CS decision problem. The EAG requested simpler NMAs at the clarification stage which the company provided and which the EAG considered appropriate, notwithstanding the wrong dose of secukinumab (no loading dose) being used as the comparator
Were NMA methods appropriate?	Yes	The company performed a series of Bayesian NMAs (detailed in the CS, Appendix K, NMA report). The company consider the methods used were consistent with the methods recommended in DSU TSD 2,[46] DSU TSD 3[47] and DSU TSD 4.[48] The EAG considers that the company has described their statistical approach to the NMAs comprehensively. The company's NMAs appear to have been correctly implemented using the methods described in DSU TSD 2,[46] DSU TSD 3[47] and DSU TSD 4[48]
Were all relevant effect modifiers identified appropriately?	Yes	Potential treatment effect modifiers were identified a priori by reviewing the literature (CS, Appendix K, NMA report, Section 4.5.2). Clinical advice to the EAG is that treatment effect modifiers identified appear to be appropriate
Was the presentation of NMA results appropriate?	Partly	The EAG considers that the company network included comparators and, therefore, a patient population that were not relevant to the decision problem addressed by the company and there appeared to be discrepancies between the results reported in the CS (Table 16 to Table 19) with the results reported in the NMA report (CS, Appendix K). The results reported in the NMA report are appropriate to the broader objectives for the NMA report

AE=adverse event; DSU=decision support unit; HRQoL=health-related quality of life; NMA=network meta-analysis; TSD=technical support document

8.2.2 Quality assessment of the trials included in company NMAs

The company quality assessments of all trials included in the NMAs (Centre for Reviews and Dissemination checklist[36]) are presented in the CS (Appendix D, Sub-appendix I). The EAG largely agrees with the company assessments but does not consider it appropriate to conduct statistical testing to determine if there are baseline differences.[49-51]

8.2.3 Patient characteristics and assessment of heterogeneity of trials included in the company NMAs

The company assessed the heterogeneity of the included trials (CS, Section B.3.9.3).

The company highlighted differences in the following baseline characteristics across trials: mean age, how duration of disease was reported, proportion of HLA-B27 positive patients, CRP levels, mean baseline BASFI score, mean baseline total back pain score, ASAS40 and ASASPR baseline risks, SPARCC MRI sacroiliac joint score and prior use of bDMARDs. In addition to differences in baseline characteristics, outcomes were measured at different timepoints across the trials, varying from 12 weeks (for five trials of all TNFα inhibitors[27-30,35] to 16 weeks for the trials of golimumab[34] and IL-17A inhibitors. The EAG considers these areas of variability may be areas of heterogeneity and hence causes for concern regarding the assumption of transitivity in the NMA.

8.2.4 Results from the NMAs conducted by the company

The company presented comparative efficacy results for six populations in the NMA report (CS, Appendix K, Section 5.4 and sub-appendix F):

1. NMA 1 ("Full population" in CS, Table 16 to Table 19): nr-axSpA patients with or without OSI, prioritising data for OSI patients where data is available for those with OSI; week 14 outcomes for upadacitinib
2. NMA 2: nr-axSpA patients with or without OSI, prioritising data for OSI patients where data is available for those with OSI; week 12 outcomes for upadacitinib
3. NMA 3 ("OSI population" in CS, Table 16 to Table 19): nr-axSpA patients with OSI; week 14 outcomes for upadacitinib
4. NMA 4: nr-axSpA patients with OSI; week 12 outcomes for upadacitinib
5. NMA 5: nr-axSpA patients with or without OSI, prioritising data for all patients over the OSI population; week 14 outcomes for upadacitinib
6. NMA 6: nr-axSpA patients with or without OSI, prioritising data for all patients over the OSI population; week 12 outcomes for upadacitinib.

In the main body of the CS, the company presented results for NMA 1 and NMA 3. NMA 3 is considered the primary NMA in the CS as it aligns with the population addressed in the decision problem. NMA 1 is included for completeness as it was informed by more trial data ([redacted] patients overall as opposed to [redacted] patients in NMA 1).

The results presented by the company for the seven outcomes/six populations, showed no statistically significant differences between upadacitinib and ixekizumab or upadacitinib and secukinumab. The results for upadacitinib versus secukinumab with a loading dose are similar to the results for ixekizumab versus secukinumab without a loading dose. There were some statistically significant differences between upadacitinib and TNFα inhibitors (favouring

certolizumab pegol and golimumab) for this appraisal (CS, Table 16 to Table 19 and Appendix K, Section 5.4 and sub-appendix F).

The EAG highlights that the results presented in the CS (Table 16 to Table 19) are presented for upadacitinib versus ixekizumab Q4W and for upadacitinib versus secukinumab without a loading dose. NICE only recommends secukinumab with a loading dose.[13] All results (including for upadacitinib versus secukinumab with a loading dose) are presented in the NMA report provided in CS, Appendix K. The EAG further noticed discrepancies between the results presented in the main body of the CS (Table 16 to Table 19) and CS, Appendix K, Section 5.4 and sought clarification from the company (Clarification Question A7). The corrected results for upadacitinib presented during clarification and also in the CS, Appendix K for upadacitinib versus both doses of ixekizumab and for upadacitinib versus both doses of secukinumab are summarised in Table 11 and Table 12.

The company concluded (CS, p47 and p72) that “upadacitinib has comparable efficacy to IL-17A inhibitors for the treatment of active nr-axSpA.” The EAG considers that it can only be concluded that there are no statistically significant differences; this is not the same as concluding efficacy is comparable, particularly when the credible intervals are wide, as is the case with all the non-statistically significant results presented by the company.

Table 11 Results from company NMAs: upadacitinib versus comparator, patients with OSI only, median (95% credible interval) (NMA3)

Outcome	Placebo	IXE Q2W	IXE Q4W	SEC (LD)	SEC (no LD)
ASAS20 (OR)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASAS40 (OR)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASASPR (OR)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI50 (OR)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI CFB (MD)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASFI CFB (MD)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TBP CFB (MD)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] OR>1.00, result favours upadacitinib
[b] MD<0.00, results favour upadacitinib
ASAS20=assessment of ankylosing spondylitis 20; ASAS40=assessment of ankylosing spondylitis 40; ASASPR= assessment of ankylosing spondylitis partial remission; BASDAI50=Bath ankylosing spondylitis disease activity index 50, BASFI=Bath ankylosing spondylitis functional index; CFB=change from baseline; IXE=ixekizumab; MD=mean difference; OR=odds ratio; LD=loading dose; Q2W=every 2 weeks; Q4W=every 4 weeks; SEC=secukinumab; TBP=total back pain
Source: NMA report (CS, Appendix K)

Table 12 Results from company NMAs: upadacitinib versus comparator, full population (patients with and without OSI), median (95% credible interval) (NMA1)

Outcome	Placebo	IXE Q2W	IXE Q4W	SEC (LD)	SEC (no LD)
ASAS20 (OR)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASAS40 (OR)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASAPR (OR)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI50 (OR)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI CFB (MD)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASFI CFB (MD)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TBP CFB (MD)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] OR>1.00, result favours upadacitinib
[b] MD<0.00, results favour upadacitinib
ASAS20=assessment of ankylosing spondylitis 20; ASAS40=assessment of ankylosing spondylitis 40; ASASPR= assessment of ankylosing spondylitis partial remission; BASDAI50=Bath ankylosing spondylitis disease activity index 50, BASFI=Bath ankylosing spondylitis functional index; CFB=change from baseline; IXE=ixekizumab; LD=loading dose; MD=mean difference; OR=odds ratio; Q2W=every 2 weeks; Q4W=every 4 weeks; SEC=secukinumab; TBP=total back pain
Source: NMA report (CS, Appendix K)

8.2.5 EAG comment on the NMAs presented in the CS

Overall, the EAG considers the company NMA methods were appropriate. However, the EAG considers that a network that only included trials of the bDMARDs of interest (upadacitinib, ixekizumab and secukinumab) in the population of interest (patients with nr-axSpA that is not controlled well enough with NSAIDs and who are not able to tolerate or achieve an adequate response to TNFα inhibitors) would be more appropriate for decision making. Therefore, the EAG asked the company to conduct NMAs using data from only the SELECT-AXIS 2, COAST-X and PREVENT trials (Clarification Question A7).

8.3 Appendix 3 Eligibility criteria and patient characteristics of the SELECT-AXIS 2, COAST-X and PREVENT trials

Eligibility criteria and baseline characteristics are summarised in Table 13 and Table 14.

Table 13 Summary of SELECT-AXIS 2, COAST-X and PREVENT eligibility criteria

Criteria	SELECT-AXIS 2	COAST-X	PREVENT
Included	• ≥18 years • male or female • Clinical diagnosis of nr-axSpA meeting the 2009 ASAS classification criteria for AS (IBP≥6 months, disease onset at <45 years of age, and sacroiliitis on MRI with ≥1 SpA feature or HLA-B27 positive with ≥2 SpA features) but not the radiologic criterion of the modified New York criteria for AS • Patients with or without prior exposure to a bDMARD (treatment with ≤1 bDMARD, 1 TNFα inhibitor or 1 IL-17A inhibitor and patients must have discontinued bDMARD because of tolerability or efficacy issues) • Objective signs of nr-axSpA active inflammation on MRI of sacroiliac joints or hsCRP >ULN (5mg/L) at Screening • BASDAI score ≥4 and total back pain score ≥4 based on a 0 to 10 NRS at screening and baseline visits	• ≥18 years • male or female • Clinical diagnosis of nr-axSpA meeting the 2009 ASAS classification criteria for AS (IBP≥6 months, disease onset at <45 years of age, and sacroiliitis on MRI with ≥1 SpA feature or HLA-B27 positive with ≥2 SpA features) but not the radiologic criterion of the modified New York criteria for AS • History of back pain≥3 months with age onset <45 years • Objective signs of nr-axSpA active inflammation on MRI of sacroiliac joints or hsCRP >ULN (5mg/L) at Screening • BASDAI score ≥4, spinal pain (BASDAI Question 2) ≥4 and total back pain score ≥4 based on a 0 to 10 NRS at screening and baseline visits • ≥2 NSAIDs at therapeutic dose range for ≥4 weeks with an inadequate or failed response or tolerability issues	• ≥18 years • male or female • Clinical diagnosis of nr-axSpA meeting the 2009 ASAS classification criteria for AS (IBP≥6 months, disease onset at <45 years of age, and sacroiliitis on MRI with ≥1 SpA feature or HLA-B27 positive with ≥2 SpA features) but not the radiologic criterion of the modified New York criteria for AS • Patients with or without prior exposure ≤1 TNFα inhibitor; patients must have discontinued because of tolerability or efficacy issues • Objective signs of nr-axSpA active inflammation on MRI of sacroiliac joints or hsCRP >ULN (5mg/L) at Screening • BASDAI score ≥4, spinal pain (BASDAI Question 2) ≥4 and total back pain score ≥40mm based on a 0 to 10 VAS at screening and baseline visits • ≥2 NSAIDs at highest recommended dose for ≥4 weeks with an inadequate or failed response or tolerability issues
Excluded	• Patients with an adequate response to TNFα and IL-17A inhibitors • Prior exposure to JAK inhibitors • History of allergic reaction or significant sensitivity to the same drug class • Extra-articular manifestations (including psoriasis, uveitis, or IBD) that were not clinically stable for ≥30 days prior to study entry	• Patients with prior exposure to bDMARDs • History of allergic reaction or significant sensitivity to the same drug class • Active Crohn's disease or ulcerative colitis. Patients may be enrolled if they had a history of IBD if they had had no exacerbation and were on stable treatment for ≥6 months • Active anterior uveitis (acute) <42 days prior to baseline	• Patients with an adequate response to TNFα inhibitors • Prior exposure to secukinumab or any other IL-17A inhibitor • History of allergic reaction or significant sensitivity to the same drug class • Active extra-articular manifestations (including psoriasis, uveitis, or IBD)

AS=ankylosing spondylitis; ASAS=assessment of ankylosing spondylitis; BASDAI=Bath Ankylosing Spondyloarthritis Disease Activity Index; bDMARDs=biologic disease modifying anti-rheumatic drugs; HLA-B27= human leukocyte antigen B27; hsCRP=high sensitivity C-reactive protein; IBD=inflammatory bowel disease; IBP=inflammatory back pain; IL-17A=interleukin 17A; JAK=Janus kinase; MRI=magnetic resonance imaging; nr-axSpA=non-radiographic spondyloarthritis; NRS=numerical rating scale; NSAID=non-steroidal anti-inflammatory drug; SpA=spondyloarthritis; TNFα=tumour necrosis factor-alpha; ULN=upper limit of normal; VAS=visual analogue scale
Source: CS, Table 8, Deodhar 2020[17] and Deodhar 2021[18]

Table 14 Summary of SELECT-AXIS 2, COAST-X and PREVENT baseline characteristics

	SELECT-AXIS 2		COAST-X			PREVENT		
	PBO (n=157)	UPA (n=156)	PBO (n=105)	IXE Q2W (n=102)	IXE Q4W (n=96)	PBO (n=186)	SEC (n=185)	SEC (no LD) (n=184)
Age, years, mean (SE)	42.50 [redacted]	41.60 [redacted]	39.90 (1.21)	40.00 (1.19)	40.90 (1.48)	39.30 (0.84)	39.10 (0.84)	39.80 (0.86)
Male, n (%)	63 (40.1)	67 (42.9)	44 (41.9)	49 (48.0)	50 (52.1)	91 (48.9)	80 (43.2)	84 (45.7)
Diagnosis duration (years), mean (SE)	4.35 [redacted]	4.55 [redacted]	3.10 (0.44)	3.40 (0.46)	4.20 (0.56)	2.96 (0.37)	2.75 (0.34)	2.12 (0.22)
Symptoms duration (years), mean (SE)	9.20 [redacted]	9.00 [redacted]	10.10 (0.81)	10.60 (1.00)	11.30 (1.09)	8.39 (0.61)	8.72 (0.68)	8.57 (0.64)
CRP (mg/L), mean (SE)	[redacted]	[redacted]	14.30 (2.38)	12.10 (1.76)	12.40 (1.84)	10.76 (1.56)	13.17 (2.00)	9.67 (1.17)
CRP+, n (%)	84 (53.5)	99 (63.5)	57 (54.3)	57 (55.9)	55 (57.3)	105 (56.5)	104 (56.2)	107 (58.2)
HLA-B27, n (%)	93 (59.2)	90 (57.7)	77 (73.3)	73 (71.6)	71 (74.0)	129 (69.4)	136 (73.5)	117 (63.6)
BASFI (0-10), mean (SE)	5.99 [redacted]	5.89 [redacted]	6.70 (0.20)	6.50 (0.18)	6.40 (0.21)	5.89 (0.14)	6.24 (0.15)	5.92 (0.15)
BASDAI (0-10), mean (SE)	6.91 [redacted]	6.82 [redacted]	7.20 (0.15)	7.30 (0.13)	7.00 (0.15)	6.76 (0.09)	7.08 (0.10)	6.93 (0.11)
Total Back Pain (0-10), mean (SE)	7.30 [redacted]	7.20 [redacted]	7.40 (0.16)	7.40 (0.16)	7.30 (0.17)	7.09 (0.09)	7.33 (0.10)	7.20 (0.11)
SI MRI+, n (%)	66 (42.0)	70 (44.9)	78 (74.3)	73 (71.6)	66 (68.8)	139 (74.7)	132 (71.4)	134 (72.8)
Concomitant NSAID, n (%)	113 (72.0)	121 (77.6)	96 (91.4)	95 (93.1)	81 (84.4)	156 (83.9)	154 (83.2)	153 (83.2)
Concomitant csDMARD, n (%)	50 (31.9)	41 (26.3)	36 (34.3)	42 (41.2)	40 (41.7)	52 (28.0)	46 (24.9)	39 (21.2)
Concomitant glucocorticoid, n (%)	17 (10.8)	18 (11.5)	14 (13.3)	20 (19.6)	8 (8.3)	17 (9.1)	14 (7.6)	17 (9.2)
bDMARD-experienced, n (%)	54 (34.4)	49 (31.4)	0 (0.0)	0 (0.0)	0 (0.0)	15 (8.1)	21 (11.4)	18 (9.8)
OSI+, n (%)	157 (100.0)	156 (100.0)	105 (100.0)	102 (100.0)	96 (100.0)	186 (100.0)	185 (100.0)	184 (100.0)

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; bDMARD=biologic disease-modifying anti-rheumatic drug; csDMARD= conventional synthetic disease-modifying anti-rheumatic drug; CRP=C-reactive protein; HLA-B27= human leukocyte antigen B27; IXE=ixekizumab; LD=loading dose; NSAID=nonsteroidal anti-inflammatory drug; OSI=objective signs of inflammation; Q2W=every 2 weeks; Q4W=every 4 weeks; SE=standard error; SEC=secukinumab; SI MRI=sacroiliac joint inflammation on magnetic resonance imaging; UPA=upadacitinib

Source: CS, Appendix K, Sub-appendix A, Table 59 and Table 60

8.4 Appendix 4 NMA inputs: individual trial results

The NMA inputs for each outcome are summarised in Table 15.

Table 15 Summary of SELECT-AXIS 2, COAST-X and PREVENT trial result inputs

Endpoint	SELECT-AXIS 2 Week 14		COAST-X Week 16			PREVENT Week 16		
	PBO (n=157)	UPA (n=156)	PBO (n=105)	IXE Q2W (n=102)	IXE Q4W (n=96)	PBO (n=186)	SEC (n=185)	SEC (no LD) (n=184)
ASAS20								
N assessed	157	156	--	--	--	186	185	184
N responded	69	104	--	--	--	85	105	107
%*	43.9%	66.7%	--	--	--	45.7%	56.8%	58.2%
ASAS40								
N assessed	157	156	105	102	96	186	185	184
N responded	35	70	20	41	34	52	74	75
Proportion*	22.3%	44.9%	19.0%	40.2%	35.4%	28.0%	40.0%	40.8%
ASASPR								
N assessed	[redacted]	[redacted]	--	--	--	186	185	184
N responded	[redacted]	[redacted]	--	--	--	13	40	39
Proportion*	[redacted]	[redacted]	--	--	--	7.0%	21.6%	21.2%
BASDAI50								
N assessed	157	156	105	102	96	186	185	184
N responded	35	66	15	34	30	39	69	69
Proportion*	22.3%	42.3%	14.3%	33.3%	31.3%	21.0%	37.3%	37.5%
BASDAI CFB								
Endpoint N	[redacted]	[redacted]	105	102	96	186	185	184
Mean (SE)	[redacted]	[redacted]	-1.510 (0.220)	-2.520 (0.220)	-2.180 (0.220)	-1.460 (0.210)	-2.350 (0.200)	-2.430 (0.200)
BASFI CFB								
Endpoint N	156	154	105	102	96	186	185	184
Mean (SE)	-1.470 [redacted]	-2.610 [redacted]	-1.340 (0.230)	-2.280 (0.230)	-2.010 (0.230)	-1.010 (0.210)	-1.750 (0.200)	-1.640 (0.200)
Total Back Pain CFB								
Endpoint N	[redacted]	[redacted]	99	98	96	171	164	166
Mean (SE)	-2.000 [redacted]	-2.910 [redacted]	-1.500 (0.240)	-2.600 (0.240)	-2.400 (0.250)	-2.027 (0.219)	-3.093 (0.223)	-3.191 (0.222)

* %s added for information only, these data not input into NMAs

ASAS20=assessment of ankylosing spondylitis 20; ASAS40=assessment of ankylosing spondylitis 40; ASAS PR=assessment of ankylosing spondylitis partial remission; BASDAI50=Bath ankylosing spondylitis disease activity index 50, BASFI=Bath ankylosing spondylitis functional index; CFB=change from baseline;

Source: CS, Appendix K, Sub-appendix A, Table 61 and Table 62