Technology Appraisal

Upadacitinib for treating active non-radiographic axial spondyloarthritis [ID3958]

Committee Papers

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COST-COMPARISON EVALUATION

Upadacitinib for treating active non-radiographic axial spondyloarthritis [ID3958]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission from Eli Lilly and Company**
2. **Clarification questions and company responses**
3. **Patient group, professional group, and NHS organisation submissions** from:
   a. British Society for Rheumatology
   b. National Axial Spondyloarthritis Society
4. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group
5. **External Assessment Report – factual accuracy check**

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

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Single technology appraisal: cost-comparison

Upadacitinib for treating active non-radiographic axial spondyloarthritis [ID3958]

Document B

Company evidence submission

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Abbreviations

Abbreviation	Definition
AD	Atopic dermatitis
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AO	As observed
AS	Ankylosing spondylitis
ASAS	Assessment of ankylosing spondylitis
ASDAS	Ankylosing spondylitis disease activity score
ASQoL	Ankylosing spondylitis quality of life
axSpA	Axial spondyloarthritis
BASDAI	Bath ankylosing spondyloarthritis disease activity index
BASFI	Bath ankylosing spondylitis functional index
bDMARDs	Biologic disease modifying anti-rheumatic drugs
bDMARD-IR	Biologic disease modifying anti-rheumatic drug – inadequate responder
$BASMI_{lin}$	Linear Bath Ankylosing Spondylitis Metrology Index
BMI	Body mass index
BNF	British National Formulary
BSR	British Society of Rheumatology
CEA	Cost-effectiveness analysis
CFB	Change from baseline
CI	Confidence interval
CMA	Cost-minimisation analysis
CMH	Cochran-Mantel-Haenszel
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
csDMARDs	Conventional synthetic biologic disease modifying anti-rheumatic drugs
CYP3A	Cytochrome P450, family 3, subfamily A
EAER	Exposure-adjusted event rate
EAM	Extra-articular manifestation
ERG	Evidence review group
FAS	Full analysis set
FTA	Fast-track appraisal
HI	Health index
IBD	Inflammatory bowel disease
ID	Inactive disease
IL-17A	Interleukin 17A
IRT	Interactive response technology
ITC	Indirect treatment comparison
JAK	Janus Kinase
LDA	Low disease activity
LS	Least squares
MACE	Major adverse cardiac event

MASES	Maastricht ankylosing spondylitis enthesitis score
MMRM	mixed-effect model repeat measurement
MRI	Magnetic resonance imaging
mSASSS	modified stoke ankylosing spondylitis spine score
MTA	Multiple technology appraisal
MTX	Methotrexate
NASS	National ankylosing spondylitis society
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
nr-axSpA	Non-radiographic spondyloarthritis
NRI-MI	non-responder imputation incorporating multiple imputation
NSAID	Non-steroidal anti-inflammatory drug
OSI	Objective signs of inflammation
PAS	Patient access scheme
PR	Partial remission
PSS	Personal Social Services
PSSRU	Personal Social Services Resource use
QD	Once a day
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
SAP	Statistical analysis plan
SD	Standard deviation
SAE	Serious adverse event
SI	Sacroiliac joint
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SPARCC	Spondyloarthritis Research Consortium of Canada
STATs	signal transducers and activators of transcription
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
TRAE	Treatment-related adverse event
TYK	Tyrosine kinase
UK	United Kingdom
ULN	Upper limit of normal
US	United States of America
VAS	Visual acuity score
VTE	Venous thromboembolism
WPAI	Work productivity and activity impairment

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

B.1.1 Decision problem

B.1.1.1 Population

The population considered in this appraisal are patients with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation (OSI) who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs) and who are not suitable for treatment with or whose condition is not controlled well enough by tumour necrosis factor (TNF) -α inhibitors. This patient population is in line with the population in which the IL-17A inhibitors, secukinumab (TA719[1]) and ixekizumab (TA718[2]), received positive NICE recommendations in 2021.

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. As such, the submission represents a sub-population to that specified in the NICE pre-invitation scope and the licenced indication. The decision problem addressed in this appraisal is outlined in Table 1.

B.1.1.2 Comparators

B.1.1.2.1 NICE HTA guidance

The NICE cost-comparison route is suggested for the appraisal of upadacitinib. According to NICE guidance, if a health technology is likely to provide similar or increased health benefits at similar or lower costs compared to health technologies previously recommended in the same indication then a cost comparison can be conducted.[3]

A cost comparison must include all relevant comparators recommended for the same indication, which adequately represent the NICE recommended treatments, both in terms of costs and effects. Therefore, when identifying comparators for upadacitinib for the treatment of nr-axSpA, these comparators must represent the current treatment pathway recommended for the population under consideration.

nr-axSpA is part of the disease spectrum of axial spondyloarthritis and therefore, is related to ankylosing spondylitis (AS), for which upadacitinib is currently being appraised. Please note that on 27th April 2022, NICE confirmed that the AS appraisal has been accepted for assessment via the cost-comparison route. Given the similar disease area and comparative treatments, and the justifications provided below, we anticipate that this appraisal will also meet the criteria the cost-comparison process.

B.1.1.2.2 NICE recommended treatments and final comparators

The population addressed in the appraisal for upadacitinib for the treatment of nr-axSpA is patients with OSI who have responded inadequately to NSAIDs and who are not suitable for treatment with or whose condition is not controlled well enough by TNF-α inhibitors. This aligns with clinical advice given to AbbVie regarding where upadacitinib would be positioned in the current clinical pathway, as discussed in Section B.1.3.[4]

Currently, patients with OSI who have responded inadequately to NSAIDs and who are not suitable for treatment with or whose condition is not controlled well enough by TNF-α inhibitors are offered the IL-17A inhibitors, secukinumab and ixekizumab (Section B.1.3.4). Therefore, as these treatments are recommended in the same patient population by NICE, secukinumab and ixekizumab are considered the relevant comparators for upadacitinib in this patient population. This was also confirmed by clinical expert feedback during interviews conducted by AbbVie.[4] Additionally, IL-17A inhibitors are not suitable for patients with co-existing extra-articular manifestations including inflammatory bowel disease (IBD).[5] Consequently, there is a significant unmet need in these patients for an alternative treatment, as discussed in Section B.1.3.3.

While the NICE scope includes a broad range of comparators for the treatment of active nr-axSpA, this appraisal only covers a subgroup of this population. Therefore, only the comparators that are recommended for this subgroup are considered as relevant comparators for upadacitinib, namely, secukinumab and ixekizumab. During interviews conducted by AbbVie, clinicians stated that they were very unlikely to offer patients established clinical management, which consists of NSAIDs and physiotherapy, at this stage of their disease progression. As these patients have

already failed to achieve an adequate response to NSAIDs and clinicians would recommend an alternative biologic treatment.[4] Therefore, established clinical management is not considered a relevant comparator for this appraisal.

Both secukinumab and ixekizumab were recently recommended for use in the same patient population,[1,2] and therefore, fully represent NICE recommended treatment for this patient population, in line with NICE guidelines for selecting comparators and in alignment with the requirements of cost-comparison appraisal to provide similar health benefits and costs.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with active non-radiographic axial spondyloarthritis	Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation that is not controlled well enough with NSAIDs and who are not able to tolerate or achieve an adequate response to TNFα inhibitors.	The patient population addressed in this submission represents a subgroup of the population specified in the NICE pre-invitation. This aligns with the anticipated license for upadacitinib and the population in which the IL-17A inhibitors (secukinumab and ixekizumab) have been recommended. The anticipated licence wording for upadacitinib in this indication is for the treatment of active non-radiographic axial spondyloarthritis (nr-axSpA) in adult patients with objective signs of inflammation who have responded inadequately to NSAIDs.
Intervention	Upadacitinib	Upadacitinib	As per NICE scope
Comparator(s)	IL-17A inhibitors • Secukinumab • Ixekizumab TNFα inhibitors: • Adalimumab • Certolizumab pegol • Etanercept • Golimumab Established clinical management without biological treatments	IL-17A inhibitors • Secukinumab • Ixekizumab	The NICE scope includes a broad range of treatments for nr-axSpA. However, the patient population that will be addressed in the submission is in line with the population in which the IL-17A inhibitors received a positive NICE recommendation, as stated above. Secukinumab and ixekizumab fulfil the criteria for comparator selection as outlined in Section B.1.1.2 and adequately represent the NICE recommended treatments as a whole, in terms of cost and effect for this indication.

Outcomes	The outcome measures to be considered include: • disease activity • functional capacity • disease progression • pain • peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • adverse effects of treatment • health-related quality of life	The main outcome measures which are in line with the NICE draft scope and previous IL-17A inhibitor appraisals will include: • disease activity (ASAS 40, BASDAI 50) • functional capacity (BASFI) • total back pain • adverse effects of treatment	The NICE scope also lists peripheral symptoms and symptoms of extra-articular manifestations as outcome measures to be considered. These outcome measures are not applicable to this appraisal, given the proposed cost-comparison analysis comparing to the IL-17A inhibitors, secukinumab and ixekizumab, which did not report these outcomes in their respective clinical trial results and NICE appraisals.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or	A cost-comparison model is being developed in Excel to evaluate the cost to the NHS associated with the use of upadacitinib versus ixekizumab and secukinumab in treating the patient population defined above. • An appropriate time horizon will be adopted to capture any differences in costs between the technologies being appraised • All costs will be discounted at a rate of 3.5% per year in alignment with the NICE guide to the methods of technology appraisal • Costs will be considered from an NHS and personal social services (PSS) perspective	As per NICE scope

	outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.		
Subgroups to be considered	Not specified	No specified subgroups were identified for analysis.	As per NICE scope
Special considerations including issues related to equity or equality	The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The cost-comparison focuses on upadacitinib and ixekizumab or secukinumab as the comparators. Drug acquisition costs were sourced from the BNF; no biosimilar or generic agents are available for either of the key comparators.	As per NICE scope

B.1.2 Description of the technology being evaluated

Table 2 presents a description of Upadacitinib [RINVOQ®], the technology being evaluated in this submission. The Summary of Product Characteristics and European Public Assessment Report are attached in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Upadacitinib (RINVOQ®)
Mechanism of action	Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.[6] Janus Kinases (JAKs) are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis and immune surveillance. The JAK family of enzymes contains four members: JAK1, JAK2, JAK3 and TYK2, which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation modulates gene expression and cellular function. JAK1 is important in inflammatory cytokine signals.
Marketing authorisation/CE mark status	[redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication is for the treatment of active non-radiographic axial spondyloarthritis (nr-axSpA) in adult patients with objective signs of inflammation who have responded inadequately to NSAIDs. Upadacitinib is currently indicated for rheumatoid arthritis, psoriatic arthritis and atopic dermatitis (15 mg or 30 mg in adults dependent on presentation and 15 mg for adolescent populations).[6] Upadacitinib for the treatment of ankylosing spondylitis is currently going through the NICE appraisal process.
Method of administration and dosage	Oral administration 15 mg prolonged-release tablet once daily with or without food and may be taken at any time of day
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment	Upadacitinib (RINVOQ®) 15 mg tablets Unit price: £28.77 Pack of 28 tablets: £805.56

	Annual maintenance treatment at 15 mg: £10,508.24 Treatment discontinuation should be considered in patients who show no clinical response after 16 weeks of treatment. Some patients with initial partial response may improve with continued treatment beyond 16 weeks.[6] Estimates are based on patients receiving one tablet per day for 365.25 days per year.
Patient access scheme/commercial arrangement (if applicable)	Upadacitinib (RINVOQ®) 15 mg tablets Unit price: [redacted] Pack of 28 tablets: [redacted] Annual maintenance treatment at 15 mg: [redacted]
JAK: Janus kinase; STATs: signal transducers and activators of transcription; TNFα: tutor necrosis factor alpha Source: EMA RINVOQ® Summary of Product Characteristics[6]	

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

B.1.3.1 Disease overview

Axial spondyloarthritis is a chronic inflammatory disease that is part of a heterogeneous group of inflammatory rheumatological diseases affecting the spine and sacroiliac joints.[7] Consequently, patients with axial spondyloarthritis experience back pain, arthritis, enthesitis and fatigue as well as extra-articular manifestations (EAMs) such as uveitis, inflammatory bowel disease and psoriasis.[7] The condition is currently incurable and causes irreversible damage.[8]

Axial spondyloarthritis is considered a spectrum of diseases that includes radiographic (r-axSpA usually referred to as ankylosing spondylitis, AS) and non-radiographic axial spondyloarthritis (nr-axSpA). For nr-axSpA, inflammation is not detectable radiographically but is identifiable through other signs of inflammation including C-reactive protein and magnetic resource imaging.[7] It is estimated that 56% of axial spondyloarthritis patients have AS and 44% present with nr-axSpA.[9,10] In addition, it is estimated that over a 2 to 10 year time period, between 10% to 40% of patients progress from nr-axSpA to AS.[11] However, this does not indicate that the non-radiographic form is less severe as the disease burden of AS and nr-axSpA is similar, especially in terms of disease activity, pain and quality of life (QoL) impairment.[12]

B.1.3.2 Epidemiology

The onset of nr-axSpA most commonly occurs between the ages of 20 to 30 years[13] with approximately 95% of patients aged below 45 years when symptom onset commences.[8] With an estimated ratio of 10:1, axial spondyloarthritis was once considered to predominantly affect men, however more recently, sex prevalence has since been determined to be similar,[14] with an equal ratio of men and women affected by nr-axSpA.[15]

The prevalence of nr-axSpA is largely undetermined, which is partly due to an average diagnostic delay of 8.5 years,[13,16,17] as recently highlighted in the NASS review: A Gold Standard Time to diagnosis.[13] This diagnostic delay can have a huge impact on a patient's life, can reduce the chances of a successful treatment response and can worsen disease outcomes contributing to the decreased quality of life (QoL) and psychological and social impacts on patients.[13] Additionally, this diagnostic delay costs on average over £196,000 per person, of which £121,515 per person is attributed to productivity losses over 8.5 years. This is due to undiagnosed patients losing income from unemployment, taking unpaid sick-leave or being forced to change jobs. Lack of early diagnosis translates to an increased cost of £7,106 per person to the NHS.[18] Approximately 220,000 adults have received an axial spondyloarthritis diagnosis in the UK,[8] of which an estimated 165,000 are thought to have nr-axSpA.[19,20]

B.1.3.3. Disease burden and unmet need

Recent evidence shows that nr-axSpA and AS can be considered as an 'artificial split' of a single disease entity,[21] reinforced by their similar disease characteristics.[22] The treatment options available for both diseases should be equal due to their comparable disease burden.[21]

Many patients with nr-axSpA fail to achieve adequate pain management.[23] Chronic lower back pain is the primary symptom experienced by patients, with 70% of nr-axSpA patients reporting they suffer from back pain or joint pain/inflammation daily.[24] However, with between 3 and 7 million consultations regarding back pain in the UK annually, the potential to misdiagnose or to delay diagnosis of nr-axSpA is large.[13] This delayed or misdiagnosis has been linked to worsening outcomes and quality of

life.[24] Therefore, the reduction of back pain in nr-axSpA is a main focus for both healthcare professionals and patients.

Patients living with nr-axSpA experience a significant disease burden affecting QoL.[22] Physical impairments caused by the disease can impact a patient's ability to complete everyday tasks, influencing their psychological and social well-being.[8,25] It is reported that 59% of axial spondyloarthritis patients experience mental health problems.[8] A further contributing factor to nr-axSpA patients impaired QoL is the early disease onset, where the average age of symptom onset is 24 years,[8] therefore, largely impacting key life events including careers and relationships.[26]

Remission is the ultimate treatment goal for both healthcare professionals and patients. However, despite recent advances in treatments for nr-axSpA many still do not achieve long term management, highlighting an important unmet need within this patient population for a treatment that improves patient quality of life.[27]

An additional unmet need exists in regards to mode of administration as secukinumab and ixekizumab are administered via subcutaneous injection. The once daily oral administration of upadacitinib may provide greater convenience to patients, such as when travelling or at work. Currently, there is not an alternative administration route for patients with needle phobia or dexterity issues, therefore, upadacitinib can provide relief for these patients, fulfilling this unmet need.

B.1.3.4 Current pathway of care

The current nr-axSpA treatment pathway endeavours to relieve symptoms and help control disease progression.[28] Patients presenting with signs of inflammation consistent with nr-axSpA are treated with established clinical management, which consists of NSAIDs and physiotherapy with the aim to reduce patient pain.[28,29]

Despite their widespread use and efficacy as a first-line treatment, continuous treatment with NSAIDs can be associated with hypertension, abdominal pain and cardiovascular and renal related side-effects.[30-32] Additionally, gastrointestinal symptoms, which include nausea, dyspepsia and diarrhoea, occur in 10% to 60% of patients using NSAIDs.[33] Due to this profile, NSAIDs are only prescribed on-demand for short periods in other diseases. While using NSAIDs to treat nr-axSpA has proven

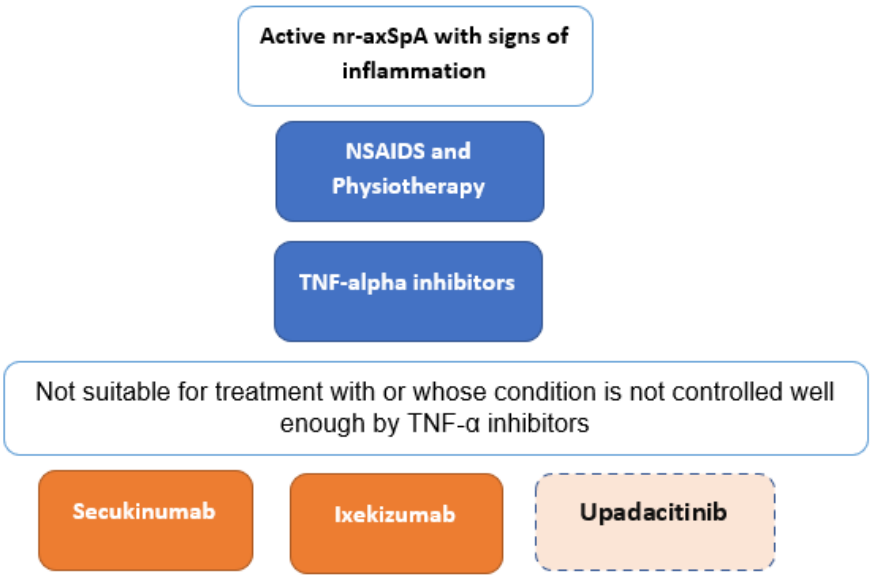
efficient to manage symptoms, their long term safety profile and their effect on radiographic progression has been questioned, as NSAIDs primarily operate by managing symptoms opposed to modifying radiographic disease progression.[34]

In the instance of an inadequate response or tolerability issues to established clinical management, biologic disease modifying anti-rheumatic drugs (bDMARDs) are recommended.[28] TNFα inhibitors, a type of bDMARD that includes adalimumab, certolizumab pegol, etanercept, golimumab and infliximab, are recommended as the next line of treatment.[29]

Switching TNFα inhibitors is frequent in nr-axSpA, often due to lack of efficacy and loss of initial response.[35] A British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS) registry prospective cohort study conducted in nr-axSpA patients (n=1,145) in the UK, found that within the first year of TNFα inhibitor treatment, around a third of nr-axSpA patients do not reach a low disease state (ASDAS <2.1), demonstrating that not all patients achieve an adequate response to TNFα inhibitors.[36] This study found that 34% of nr-axSpA patients terminated their first TNFα inhibitor due to adverse events highlighting that tolerability of TNFα inhibitors can be an issue for some patients.[36] Similarly, a US real-world evidence study of nr-axSpA patients reported similar reasoning for TNFα inhibitor switching. This highlights that nr-axSpA patients frequently switch treatments when they fail to achieve and maintain an adequate treatment response over a sustained period or if they experience tolerability issues.[35]

The IL-17A inhibitors, secukinumab[1] and ixekizumab[2] are currently recommended for patients who are not suitable or whose disease is not controlled sufficiently by TNFα inhibitors. The current nr-axSpA treatment pathway is illustrated in Figure 1.

Figure 1. Current nr-axSpA treatment pathway based on NICE guidelines[28]



NSAIDs: non-steroidal anti-inflammatory drugs; nr-axSpA: non-radiographic axial spondyloarthritis; TNFa: tumour necrosis factor alpha

B.1.3.5 Limitations in current treatment pathway

Currently, patients who fail to achieve an adequate response with TNFα inhibitors may be prescribed another TNFα inhibitor with the same mechanism of action.[28] However, as discussed above, treatment with an alternative TNFα inhibitor after previous non-response is significantly less likely to be successful.[37] Therefore, switching to a treatment with a different mechanism of action is preferred. Overall, treatment options are limited as the current nr-axSpA treatment pathway consists of only two classes of biologics after failure with NSAIDs, TNFα inhibitors and IL-17A inhibitors. Therefore, there is a significant unmet need for treatment options with new mechanisms of action for the treatment of nr-axSpA.

Additionally, patients with co-existing inflammatory bowel disease (IBD), which is experienced by approximately 7% of nr-axSpA patients,[21] are not suitable for treatment with IL-17A inhibitors,[5] due to potential worsening or the development of IBD with their use.[5,38] Therefore, these patients can only be treated with TNFα inhibitors, further highlighting the unmet need for additional treatments as they are unable to be treated with IL-17A inhibitors.

Upadacitinib, which is the first once daily JAK inhibitor licenced for nr-axSpA patients, offers an alternative mechanism of action for patients and clinicians when making treatment decisions. During interviews conducted by AbbVie, clinical experts highlighted that the new mechanism of action of upadacitinib for nr-axSpA treatment offers an additional advantage through increasing the number of treatment options available and therefore, increasing treatment choice for both clinicians and patients. The clinicians also highlighted that upadacitinib's short half-life compared to a number of advanced therapies makes it suitable for the treatment of patients with recurring infections or a history of severe infections.[4]

Both secukinumab and ixekizumab are administered via subcutaneous injection, and therefore, require additional healthcare resources and training. Upadacitinib is administered as a once daily oral tablet, which is more convenient for patients. Clinical experts stated that an oral treatment would be advantageous to nr-axSpA patients in terms of travelling and work due to it being a more convenient mode of administration.[4] It is also advantageous to patients with needle-phobia providing an alternative administration route and for patients with dexterity issues, who struggle to self-inject due to their condition.

In axial spondyloarthritis patients, including those with nr-axSpA, the administration route has been determined as the third most important consideration in selecting treatment, with an oral treatment being preferable for 49.9% of axial spondyloarthritis patients, compared with 32.2% of patients preferring subcutaneous injection and 17.9% selecting an intravenous-infused medication.[39] Additionally, clinical experts highlighted that patients would appreciate having a choice regarding mode of administration.[4]

B.1.4 Equality considerations

It is not anticipated that equality issues will arise with upadacitinib treatment. However, in previous technology appraisal guidance for TNFα inhibitors for AS and nr-axSpA treatment, an equality concern considering patient assessments was identified. The appropriateness of using BASDAI and spinal pain VAS scores should be taken into consideration in the presence of physical, sensory, learning or communication

difficulties that could affect a patient's response to the questionnaires, and adjustments should be made appropriately.[29]

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

B.2.1 Clinical outcomes and measures

A total of four NICE technology appraisals (TA) describing treatments for nr-axSpA were identified:

- TA383 (2016): TNFα inhibitors for AS and nr-axSpA (replacing TA233 and TA143)
- TA497 (2018): Golimumab, a TNFα inhibitor for treating nr-axSpA
- TA718 (2021): Ixekizumab for treating axSpA (includes both nr-axSpA and AS)
- TA719 (2021): Secukinumab for treating nr-axSpA

TA383 was a multiple technology appraisal (MTA), whilst TA718 and TA719 were single technology appraisals (STA). These submissions presented cost-effectiveness analyses as their main form of economic evidence, with the exception of TA497: golimumab for treating nr-axSpA, which opted for a fast-track appraisal (FTA) utilising a cost-comparison analysis (now known as a cost-comparison STA). This appraisal for upadacitinib uses the same cost-comparison approach as TA497.

The most common measures of clinical effectiveness used in each of the submissions were the assessment in Ankylosing Spondylitis international society 20 (ASAS20), ASAS40, Bath Ankylosing Spondylitis Disease activity index 50 (BASDAI50), BASDAI change from baseline (CFB) and Bath Ankylosing Spondylitis functional index (BASFI) CFB, defined in Table 3. These are stringent measures of response, physical function or disease activity associated with nr-axSpA. ASAS20 and ASAS40 were most frequently reported as the primary outcomes of the underlying pivotal trials, whilst BASDAI50, BASDAI CFB and BASFI CFB were used to inform cost-effectiveness modelling outcomes in the submissions. These endpoints are consistently considered as the most relevant long-term clinical outcomes for patients and were specified in the scope for previous NICE appraisals in this disease setting, as outlined in Table 4.

Table 3. Disease assessment tools and outcomes

Disease component	Outcome	Description
Physical function	BASFI	Patient assesses difficulty on a 10-point scale (1 is easy and 10 is impossible) for each of 10 items: • putting on socks or tights without help or aids • bending from the waist to pick up a pen from the floor without aid • reaching up to a high shelf without help or aids • getting up from an armless chair without hands or any other help • getting up off the floor without help from lying on back • standing unsupported for 10 minutes without discomfort • climbing 12–15 steps without using a handrail or walking aid • looking over shoulder without turning body • doing physically demanding activities • doing a full day's activities (at home or at work)
Disease activity	BASDAI	Patient describes the severity of 5 symptoms on a 10-point scale (1 is no problem and 10 is very severe): • fatigue • spinal pain • joint pain / swelling • areas of localised tenderness (also called enthesitis) • morning stiffness severity Duration of morning stiffness is also provided.
Response outcome	BASDAI 50	≥50% improvement in BASDAI score
Response outcome	ASAS 20/40	Improvement of ≥20 or 40% and ≥2 units in at least 3 of the following 4 domains (each with a 10-point scale): • patient global disease assessment • spinal pain • function (BASFI score) • inflammation (using mean score from 2 questions of the BASDAI). No worsening at all in the 4th domain.
ASAS: Assessment in Spondyloarthritis international Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index.		

Across all identified appraisals for nr-axSpA, and all commonly reported measures of clinical effectiveness, there was little evidence to suggest that any TNFα inhibitor was more effective than another,[29] or that any IL-17A inhibitor was more effective than any TNFα inhibitor.[1,2] The discussion around comparable efficacy between all treatment options is a common theme and conclusion amongst all identified appraisals, as

summarised in Table 4. An overview of the key clinical outcomes used in each of the appraisals and their use in economic evaluations is presented in Table 4 .

Beyond the key clinical outcomes, discontinuation has also been discussed during committee reviews. Across the appraisals for nr-axSpA identified, the observed unadjusted discontinuation rates informed by the pivotal trial appear to be similar across treatments.[1,2,29,40] However, none of the appraisals included discontinuation as an outcome in their approach to evidence synthesis and in their corresponding network meta-analysis (NMAs). The majority of the appraisals assumed that treatments were associated with equal rates of discontinuation beyond the initial period of treatment response (TA383: 6%, TA719: 6%, TA718: 5%). The exception to this was TA497, which did not include discontinuation in its cost-comparison analysis. Across all appraisals, the approach to discontinuation was not strongly criticised by review groups. However, with the exception of TA497 which did not include discontinuation, all review groups preferred the assumption of equal rates of discontinuation across biologic treatments. Therefore, an annual discontinuation rate of 6% has been applied to all treatments in the cost-comparison analysis presented in this appraisal, as discussed in Section B.4.2.

Table 4. Clinical outcomes and measures appraised in published NICE guidance for the comparators

Appraisal	Treatment & comparators	CEA or CMA?	Key clinical outcomes considered (A)	Statistically significant difference predicted	Used in CEA / cost-comparison?	Committee comments
TA718[2] Ixekizumab for treating axial spondyloarthritis	Ixekizumab; adalimumab; etanercept; golimumab; certolizumab pegol; infliximab; 'conventional care'	Company: CEA; ERG: CEA	ASAS40	Unclear - redacted	No	The company highlighted that the updated NMAs found no statistically significant difference between TNFα inhibitors and IL-17A inhibitors for any of the outcomes assessed. The clinical experts explained that IL-17A inhibitors are expected to have similar effectiveness to TNFα inhibitors in clinical practice, but this has not been investigated in head-to-head clinical trials.
			BASDAI 50	Unclear - redacted	Yes	
			BASDAI CFB	Unclear - redacted	Yes	
			BASFI CFB	Unclear - redacted	Yes	
TA719[1] Secukinumab for treating non-radiographic axial spondyloarthritis	Secukinumab; adalimumab; certolizumab pegol; etanercept; golimumab; 'conventional care'	Company: CEA; ERG: CEA	ASAS 20	No (B)	No	Numerical results from the network meta-analyses are confidential and cannot be reported here but point estimates for secukinumab were lower for some outcomes compared with TNFα inhibitors as a class. The committee noted that credible intervals around these estimates were wide and there were no statistically significant differences. The company stated that the clinical efficacy of secukinumab is not expected to differ substantially from TNFα inhibitors, which the clinical expert supported. The committee concluded that the results of the
			ASAS 40	No (B)	No	
			BASDAI 50	No (B)	Yes	
			BASDAI CFB	No (B)	Yes	
			BASFI CFB	No (B)	Yes	

						company's network meta-analysis were uncertain, and it could not exclude the possibility that secukinumab may be less effective than TNFα inhibitors.

ASAS: Assessment in Spondyloarthritis international Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath AS Metrology Index; CCA: cost-comparison analysis; CEA: cost-effectiveness analysis; CFB: change from baseline; ERG: external review group; IL: interleukin; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; NMA: network meta-analysis; TA: technology appraisal; TNF: tumour necrosis factor

Notes:

A: Results were presented for the 'overall AS' population and the 'biologic naïve' population; results for the 'overall AS' population are summarised here

B: Results were redacted but concluding statements described no statistically significant differences

B.2.2 Resource use assumptions

Resource use considered in the relevant NICE technology appraisals listed in Section B.2.1 include:

- Drug acquisition
- Treatment administration
- Treatment monitoring
- Disease management
- Adverse events

Across the previous STAs for treatments for nr-axSpA, there was consensus that these were the standard resources associated with the treatment of nr-axSpA and the appropriate resources required to inform an economic evaluation. TA497[41] is the only appraisal for nr-axSpA conducted by the cost-comparison process. Similar to appraisals in other disease areas assessed under the cost-comparison process, such as psoriasis,[42,43] the main resource use category has been drug acquisition costs and, where appropriate, administration costs. This approach was justified by the acknowledgement that health outcomes were deemed to be comparable across treatments, therefore, precluding any differences in disease management and adverse event cost outcomes. In each instance, the Committee agreed with these assumptions and accepted the exclusion of costs derived from health outcomes. Clinicians also agreed that disease management and adverse event cost outcomes would be comparable across biologic treatments for nr-axSpA during expert interviews conducted by AbbVie.[4]

The cost-comparison analysis presented herein focuses on the comparison of costs associated with upadacitinib, secukinumab and ixekizumab, as described in Section B1.1. Secukinumab and ixekizumab are administered via subcutaneous injection and are therefore associated with different administration costs compared to upadacitinib which is administered orally, once daily (Section B.4.2.3). Clinical feedback indicates that monitoring costs for both treatments are expected to be the same, and it is

anticipated that no additional health care infrastructure will be required with the introduction of upadacitinib.

As preferred in previous NICE technology appraisals (TA383, TA497, TA718 and TA719),[1,2,29,40] drug acquisition costs for all treatments were sourced from the British National Formulary (BNF),[44] with relevant patient access schemes (PAS) considered where appropriate. All treatments are assumed to be administered at licensed dose, based on the doses cited by the BNF,[44] relevant SmPCs[6,45,46] and those administered in pivotal studies,[47,48] ensuring that costs represent clinically feasible doses (Section B.4.2.2).

Similarly, drug administration and monitoring cost components were identified from previous NICE technology appraisals (TA383, TA497, TA718 and TA719),[1,2,29,40,41,49] and are applied consistently with these previous approaches (Section B.4.2.3). Cost data was sourced from NHS Reference Costs 2019/20,[50] previous NICE technology appraisals[2,29,49,51,52] and the PSSRU.[53]

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical and economic (non-clinical) evidence for the treatment of nr-axSpA patients including upadacitinib. Appendix D details the processes around identifying the relevant evidence.

Two searches were conducted in October 2021, the clinical search identified 4,588 records and the economic search identified 1,392 after the removal of duplicates, totalling 5,980 records. Of these, 292 studies underwent full-text review resulting in 76 records identified for inclusion in the clinical and economic SLRs.

The clinical SLR identified 65 records for inclusion, which consisted of 26 full reports, 24 conference abstracts, 14 clinical trial database entries and 1 video abstract across 6 different interventions. These 65 records described 12 individual trials (Table 5). No records for bimekizumab and upadacitinib were identified.

Table 5. Studies identified during the clinical SLR

Intervention	Full reports	Conference abstracts	Clinical trial database entries	Video abstracts	Total
Adalimumab	4	-	4	-	8
Certolizumab	9	7	2	-	18
Etanercept	6	4	3	-	13
Golimumab	2	1	2	-	5
Ixekizumab	4	5	2	-	11
Secukinumab	1	7	1	1	10
Total	**26**	**24**	**14**	**1**	**65**

B.3.2 List of relevant clinical effectiveness evidence

Evidence to support the effectiveness of upadacitinib for the treatment of active nr-axSpA is derived from the SELECT-AXIS 2, study 2 trial.

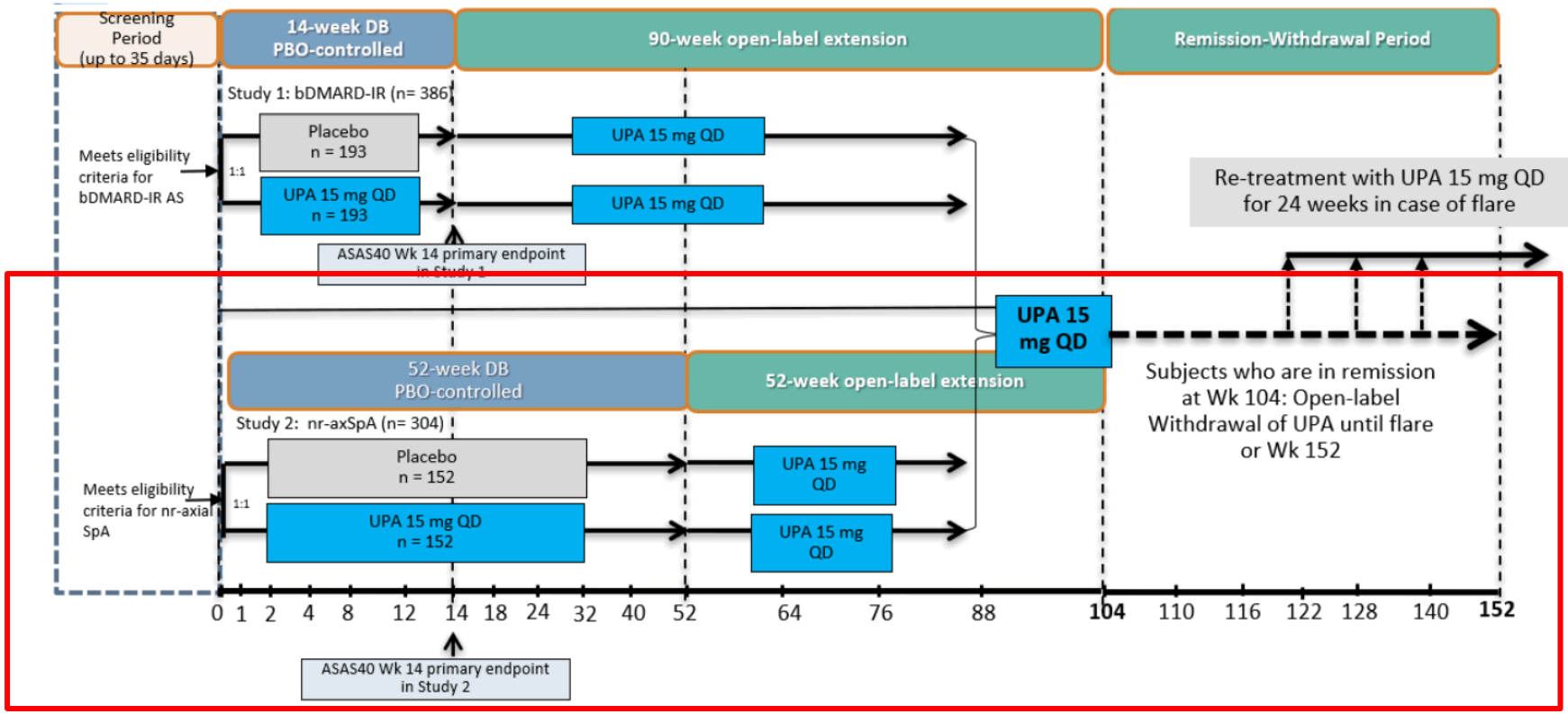
SELECT-AXIS 2 (NCT04169373) is an ongoing Phase III RCT considering the efficacy, safety and tolerability of upadacitinib in adult patients with axial spondyloarthritis, including patients with nr-axSpA. The protocol for this study includes two standalone studies with randomisation, data collection, analysis and reporting conducted independently:

1) Study 1 includes biologic experienced AS patients only (no nr-axSpA patients), meaning biologic disease-modifying antirheumatic drug inadequate responders (bDMARD-IR)

2) Study 2 includes biologic naïve and experienced nr-axSpA patients.

Please note that only patients from study 2 with nr-axSpA will be reported in this submission as study 1 includes biologic experienced AS patients only. The 304 nr-axSpA patients enrolled in study 2 received 15 mg QD of upadacitinib (n=152) or placebo (n=152). ASAS40 was the primary endpoint in the SELECT-AXIS 2 trial. A summary of SELECT-AXIS 2, study 2 is shown in **Error! Reference source not found.** and Table 6.

Figure 2. SELECT-AXIS 2 study design



AS: ankylosing spondylitis; ASAS: Assessment of SpondyloArthritis International Society; DB: double-blind; bDMARD-IR: biologic disease-modifying antirheumatic drug inadequate responder; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; PBO: placebo; QD: once daily; SI: sacroiliac; UPA: upadacitinib; Wk: week. Source: SELECT-AXIS 2 study protocol[54]

Table 6. Clinical effectiveness evidence

Study	SELECT-AXIS 2, study 2 (NCT04169373)
Study design	Phase III, multicentre, randomised, double-blind, placebo-controlled trial
Population	Patients ≥18 years with a clinical diagnosis of nr-axSpA meeting the 2009 ASAS classification criteria for axial spondyloarthritis and not meeting the radiological criterion of the modified New York criteria for AS with signs of active inflammation on MRI of SI joints or hsCRP > ULN, BASDAI ≥4 and patient's assessment of total back pain ≥4. Patients could have previous or no previous bDMARD exposure (1 TNF inhibitor or 1 IL-17 inhibitor), ≥2 NSAIDs inadequate responses across ≥4 weeks or NSAID intolerance or contraindication.
Intervention(s)	Upadacitinib 15 mg
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation (yes/no)	Yes
Reported outcomes specified in the decision problem	ASAS40 BASDAI 50 BASFI CFB Patient's Assessment of Total Back Pain CFB
All other reported outcomes	ASDAS (CRP) CFB Patient's Assessment of Nocturnal Back Pain CFB ASDAS (CRP) ID (ASDAS score < 1.3) ASDAS (CRP) LDA (ASDAS score < 2.1) ASAS PR MRI SPARCC score (SI joints) CFB ASQoL CFB ASAS HI CFB $BASMI_{lin}$ CFB MASES CFB MRI SPARCC score (spine) at week 14 CFB ASAS20 response ASDAS (CRP) MI (CFB ≤ –2.0) ASDAS (CRP) CII (CFB ≤ –1.1) Discontinuation of opioids among subjects with opioid use at Baseline
ASAS40: assessment of ankylosing spondylitis 40; ASASHI: assessment of ankylosing spondylitis health index; ASASPR: assessment of ankylosing spondylitis partial remission; ASDAS: ankylosing spondylitis disease activity score; ASQoL: ankylosing spondylitis quality of life; BASDAI: Bath ankylosing spondylitis disease activity score, BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis metrology index; bDMARDs: biologic disease-modifying antirheumatic drugs; CFB: change from baseline; CRP: C-reactive protein; MASES: Maastricht ankylosing spondylitis enthesitis score; MRI: magnetic resonance imaging; NSAIDs: non-steroidal anti-inflammatory drugs; SPARCC: Spondyloarthritis Research Consortium of Canada; Source: SELECT-AXIS 2 protocol[54]	

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

B.3.3.1 Study design

SELECT-AXIS 2, study 2 is a phase 3 multicentre, randomised, double-blind, placebo-controlled, two-period, parallel-group trial. The primary objective was to determine the efficacy, safety and tolerability of upadacitinib compared to placebo for the treatment of nr-axSpA patients. Between the two treatment arms, upadacitinib 15 mg once daily and placebo, patients were randomised in a 1:1 ratio in the double-blind period. An open label extension period, over 90 weeks for patients completing the double-blind period assessed the longer-term efficacy, safety and tolerability of upadacitinib. For patients achieving moderate-low disease activity, defined as ASDAS < 1.3 at Week 104 or ASDAS < 2.1 at Week 88, this was followed by a remission-withdrawal period to determine disease control commencing upadacitinib withdrawal. Currently only results from period 1 are available as the study is ongoing. The results from period 1 include ASAS40 at week 14, which is the primary endpoint of SELECT-AXIS 2, study 2.

Error! Reference source not found. shows the study design of SELECT-AXIS 2, study 2. An increased level of detail regarding SELECT-AXIS 2 study methodology is provided in **Error! Reference source not found.**. Section B.3.6.3 contains eligibility criteria information and Section B.3.6.4 presents the statistical methods utilised.

Table 7. SELECT-AXIS 2, study 2 trial methodology summary

Trial name	SELECT-AXIS 2, study 2 (NCT04169373)
Location	North America, South/Central America, Eastern Europe, Western Europe, Asia, Other
Trial design	Phase 3 multicentre, randomised, double-blind, placebo-controlled, two-period, parallel-group
Eligibility criteria for participants	Adults ≥18 years with a clinical diagnosis of nr-axSpA meeting the 2009 ASAS classification criteria for axial spondyloarthritis and not meeting the radiological criterion of the modified New York criteria for AS, signs of active inflammation on MRI of SI joints or hsCRP > ULN, BASDAI ≥4 and patient's assessment of total back pain ≥4, previous or no previous bDMARD exposure (1 TNF inhibitor or 1 IL-17 inhibitor) and discontinuation due to intolerance or lack of efficiency.

Trial name	SELECT-AXIS 2, study 2 (NCT04169373)
	Additional information is shown in **Error! Reference source not found.**.
Settings and locations where data were collected	113 sites in 23 countries: Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, China, Czechia, France, Germany, Hungary, Israel, Japan, Mexico, Poland, Russian Federation, Slovakia, South Korea, Spain, Taiwan, Turkey, Ukraine, United States
Study drugs	Upadacitinib 15 mg QD and placebo
Concomitant medications	csDMARDs could be continued if patients were receiving a stable dose before baseline visit for at least 28 days, up to two background csDMARDs was allowed but not the combination of methotrexate (MTX) and leflunomide. Stable doses are as followed: MTX (≤ 25 mg/week), Sulfasalazine (≤ 3 g/day), Hydroxychloroquine (≤ 400 mg/day), Chloroquine (≤ 400 mg/day), Leflunomide (≤ 20 mg/day) and Apremilast (≤ 60 mg/day). For concomitant oral corticosteroids, a stable dose of prednisone (≤ 10 mg/day) or oral corticosteroid equivalent for a minimum of 14 days prior to Baseline visit was implemented. For concomitant NSAIDs, tramadol, combination of acetaminophen/ paracetamol and codeine or combination of acetaminophen/ paracetamol and hydrocodone, and/or non-opioid analgesics a stable dose before baseline visits for the minimum of 14 days was required. Prior exposure to JAK inhibitors, intra-articular joint injections, spinal/paraspinal injection(s), or parenteral administration of corticosteroids (including intramuscular and intravenous injections), csDMARDs (except those mention previously) such as thalidomide, opioid analgesics with the exception of the combination of acetaminophen/paracetamol and codeine or combination of acetaminophen/paracetamol and hydrocodone, live vaccine, no strong cytochrome P450 3A (CYP3A) inhibitors or strong CYP3A inducers, investigational drug and allergic reaction or same drug class sensitivity were not allowed.
Primary endpoint	ASAS40 response at week 14, a 40% improvement in disease activity.
Secondary endpoints	Disease activity: • Change from baseline in ASDAS (CRP) • Proportion of patients with BASDAI 50 response (defined as 50% improvement in the BASDAI) • Change from baseline in ASAS health index • ASAS partial remission • ASAS20 • ASDAS (CRP) Inactive Disease (ASDAS score < 1.3) • ASDAS (CRP) Low Disease Activity (ASDAS score < 2.1) • Change from baseline in BASDAI Functional capacity: • Change from baseline in BASFI • Change from baseline in $BASMI_{lin}$

Trial name	SELECT-AXIS 2, study 2 (NCT04169373)
	Disease progression: • Change from baseline in SPARCC score (spine) • Change from Baseline in MRI SPARCC score (SI joints) Pain: • Covered in the ASAS and BASDAI criteria • Change from baseline in Patient's assessment of total back pain • Change from baseline in Patient's assessment of nocturnal back pain Peripheral symptoms: • Change from baseline in MASES (enthesitis) Adverse events HRQoL: • Change from baseline in ASQoL
Pre-planned subgroups	• Age (< 40, ≥ 40), • Gender (male and female), • Race (white vs non-white), • Weight, BMI (< 25, ≥ 25) • Geographical region (North America, South/Central America, Eastern Europe, Western Europe, Asia, Other) • hsCRP level at screening, • prior bDMARD exposure, • MRI (SI joints) inflammation at screening, • hsCRP/MRI SI joint inflammation at screening, • duration since nr-axSpA symptoms • duration since nr-axSpA diagnosis
ASAS: assessment of ankylosing spondylitis; ASDAS: Ankylosing spondylitis disease activity score; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; $BASMI_{lin}$: linear Bath ankylosing spondylitis metrology index; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; csDMARD: conventional synthetic disease modifying antirheumatic drug; CYP3A: cytochrome P450 3A; HI: health index; JAK: Janus kinase; MASES: Maastricht ankylosing spondylitis enthesitis score; mSASSS: modified stoke ankylosing spondylitis spine score; MRI: magnetic resonance imaging; MTX: methotrexate; NRS: numerical rating scale; NSAIDs: non-steroidal anti-inflammatory drugs; PGA: physician's global assessment of disease activity; PR: partial remission; PtGA: Patient's global assessment of disease activity; QD: once daily; SI: sacroiliac; SPARCC: spondyloarthritis research consortium of Canada; SSZ: sulfasalazine;; WPAI: work productivity and activity impairment; Source: SELECT-AXIS 2[54] protocol and SELECT-AXIS 2 CRP[55]	

B.3.3.2 Study treatments

Patients enrolled in SELECT-AXIS 2, study 2 were randomised in a 1:1 ratio between two study arms, upadacitinib 15 mg QD or placebo for a 14 week period (double-blind period).

B.3.3.3 Eligibility criteria

Error! Reference source not found. summarises the key eligibility criteria for SELECT-AXIS 2, study 2 patients.

Table 8. Key inclusion and exclusion criteria for SELECT-AXIS 2, study 2

Key inclusion criteria	Key exclusion criteria
• Adult at least 18 years, male or female at screening • Clinical diagnosis of nr-axSpA meeting the 2009 ASAS classification criteria for axial spondyloarthritis but not the radiologic criterion of the modified New York criteria for AS • Patients with or without prior exposure to a bDMARD (treatment with at most 1 bDMARD, 1 TNF inhibitor or 1 IL-17 inhibitor and patients must have discontinued bDMARD because of tolerability or efficacy issues) • Objective signs of nr-axSpA active inflammation on MRI of SI joints or hsCRP > ULN at Screening • BASDAI score ≥ 4 and total back pain score ≥ 4 based on a 0 – 10 NRS at screening and baseline visits For further details, refer to the study protocol[54]	• Patients with an adequate response to TNF and IL-17 inhibitors • Prior exposure to JAK inhibitors • A history of allergic rection or significant sensitivity to the same drug class For further details, see the study protocol[54]
ASAS: assessment of ankylosing spondylitis; bDMARDs: biologic disease-modifying antirheumatic drugs; IL: interleukin; JAK: Janus kinase; hsCRP: high sensitivity C-reactive protein; BASDAI: Bath ankylosing spondylitis disease activity index; NRS: numerical rating scale; TNF: tumour necrosis factor Source: SELECT-AXIS 2 protocol[54]	

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

B.3.4.1 Statistical analysis and definition of study groups

Statistical analysis and definition of study groups in the SELECT-AXIS 2 trial is shown in Table 9.

Table 9. SELECT-AXIS 2 statistical analysis and definition of study groups

	SELECT-AXIS 2 (NCT04169373)
Analysis populations	Full Analysis Set (FAS) includes all randomised patients who received at least one dose of study drug. The FAS was used for all efficacy and baseline analyses. Per Protocol Analysis Set represents a subset of the FAS and consists of all FAS patients who did not have any major protocol violations that impact primary efficacy analysis. The primary endpoint will be analysed in the Per Protocol analysis set. The Per Protocol analysis set will be determined prior to the respective primary analysis database lock. Safety Analysis Set consists of all patients who received at least one dose of study drug. For the Safety Analysis Set, patients were assigned to a treatment group based on the treatment actually received, regardless of the treatment randomised.
Statistical analysis of primary endpoints	Primary efficacy analysis endpoint for study 2 is an ASAS40 response at week 14 determined through the use of a composite estimate framework. This is when the week 14 primary endpoint for both studies is defined as a composite endpoint that is achieved if a subject meets the following 2 components: 1) Remain in the study and on study drug through 14 weeks; and 2) Achieve an ASAS40 response at week 14. Patents who discontinue study drug before week 14 will be classed as non-responders. All patients in the FAS will be included in the primary efficacy analysis. Comparison of the primary endpoint will be made between the upadacitinib group and the placebo group using the Cochran-Mantel-Haenszel (CMH) test adjusting for the main stratification factor. The main stratification factor is hsCRP level (≤ ULN versus > ULN). Rubin's method will be used to combine the results from the multiple datasets generated by the Multiple Imputation. For both studies, the same respective analysis will be conducted on the Per Protocol Analysis Set as a supplementary analysis. Corresponding to the composite estimate, a sensitivity analysis will be conducted. Patients who discontinue study drug prior to Week 14 will be treated as non-responders. Additional missing data including those due to COVID-19 will also be treated as non-responders. The same CMH analysis as the primary analysis will be conducted. In addition, the following supplementary analyses will be performed using the treatment policy estimate framework. The same CMH analysis as the primary analysis will be conducted including all data as observed, regardless of adherence to study drug or use of rescue, with patients missing ASAS40 response treated as non-responders. Additional sensitivity analysis using Multiple Imputation may also be conducted to handle missing ASAS40 responses.
Statistical analysis of secondary endpoints	For binary endpoints, similar analyses as for the primary endpoint will be conducted on the FAS. The primary analysis of continuous endpoints will use the hypothetical estimate framework, intending to assess the treatment effect in a hypothetical scenario where patients remain on study drug without rescue. All patients in the FAS will be included for the analysis. Comparisons between the upadacitinib group and the placebo group will be performed using the Mixed Model for Repeated Measures

	(MMRM) with treatment group, visit, and treatment-by-visit interaction as fixed effects and the corresponding Baseline value and the main stratification factor as the covariates. The same main stratification factors as in the primary endpoint analyses will be used. The MMRM model includes all longitudinal data observed for patients in the FAS, with the exception that data observed after discontinuation of study drug or use of rescue will be excluded. Supplementary analyses for continuous endpoints will be performed on the FAS including all data as observed, regardless of adherence to study drug or use of rescue, using the treatment policy estimate framework. The statistical inference will be conducted using the MMRM model including treatment, visit, and treatment-by-visit interaction as the fixed effects and the corresponding Baseline value and the main stratification factors as the covariates. The same main stratification factors as in the primary endpoint analyses will be used. For multiplicity-controlled secondary continuous efficacy variables, additional sensitivity analysis will be conducted corresponding to both the hypothetical estimate and the treatment policy estimate, where missing data will be imputed using Multiple Imputation. The imputation model will include demographics variables and Baseline disease characteristics, as well as longitudinal response observed at any other visits. The analysis of covariance (ANCOVA) model will be performed on each of the multiple imputed datasets adjusting for treatment, main stratification factor, and Baseline value. The ANCOVA results from the multiple imputed datasets will be combined using the Rubin's method.
Statistical analysis of safety endpoints	All safety analyses will be carried out for each study independently using the Safety Analysis Set for both the primary analysis and for the entire study. Analyses for Study 1 and Study 2 will be based on treatments the patients actually received. Safety will be assessed by TEAEs, physical examination, laboratory assessments, and vital signs. The descriptive summary of patients experiencing TEAEs by treatment group will be tabulated by the Medical Dictionary for Regulatory Activities primary system organ class and preferred term. In addition, summary of SAEs and TEAEs by severity and relationship to study drug as assessed by the Investigator will be provided. SAEs, severe TEAEs, or TEAEs that lead to premature study discontinuation will be listed. A similar summary will also be performed for AESIs. The observed values for vital signs, physical examination, and clinical laboratory variables at each visit will be summarised. The number and percentage of patients meeting the criteria for potentially clinically significant laboratory values will be summarised. Shift of laboratory values from Baseline to defined time points will be tabulated. Missing safety data will not be imputed. Analysis details are specified in the SAP.
Sample size and power calculation	The planned total sample size of 386 patients for this study (with a 1:1 randomization ratio for placebo and upadacitinib 15 mg) provides at least 90% power for the primary endpoint ASAS40 response of upadacitinib 15 mg versus placebo using a two-sided Chi-square test at 0.05 level. For ASAS40, the assumed response rates for upadacitinib and placebo are 24% and 6%, respectively. This sample size also provides 90% power for ASAS20, with assumed response rates for upadacitinib and placebo of 41% and 24%, respectively. In addition, this sample size provides at least 80% power for several of the multiplicity-controlled secondary endpoints including change from Baseline in ASDAS, change from Baseline in MRI SPARCC score of spine, BASDAI 50 response, ASDAS Inactive Disease, change from

	Baseline in Total Back Pain, change from Baseline in Nocturnal Back Pain, ASDAS Low Disease Activity, change from Baseline in BASFI, and ASAS PR.
Handling of missing data and participant withdrawals	Additional missing data including those due to COVID-19 will be imputed using Multiple Imputation. Patients who discontinue study drug prior to Week 14 will be treated as non-responders. Additional missing data including those due to COVID-19 will also be treated as non-responders. The same CMH analysis as the primary analysis will be conducted. In addition, the following supplementary analyses will be performed using the treatment policy estimate framework. The same CMH analysis as the primary analysis will be conducted including all data as observed, regardless of adherence to study drug or use of rescue, with patients missing ASAS40 response treated as non-responders. Additional sensitivity analysis using Multiple Imputation may also be conducted to handle missing ASAS40 responses.
ANCOVA: analysis of covariance; AO: as observed; ASAS40: assessment of ankylosing spondylitis 40; CI: confidence interval; FAS: full analysis set; LS: least squares; MI: multiple imputation; MMRM: mixed effect model repeat measurement; MNAR: missing not at random; NRI: non-responder imputation; REML: restricted maximum likelihood Source: SELECT-AXIS 2 protocol[54]	

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from the SELECT-AXIS 2, study 2 trial, a large phase III trial conducted in line with the requirements of regulatory bodies. Table 10 contains the complete quality assessment for the SELECT-AXIS 2 trial. The quality assessment of SELECT-AXIS 2, study 2 and the trials identified during the clinical SLR that were used to inform the indirect treatment comparison (ITC) in Section B.3.9 was conducted based on the Centre for Reviews and Dissemination's (CRD's) guidance; additional detail is provided in Appendix D.

The patient population and treatment pathway considered by SELECT-AXIS 2, study 2 are thought to be generalisable to routine clinical practice in the UK, confirmed by clinical experts. While study sites in the UK were included in SELECT-AXIS 2, no UK patients were recruited in study 2, which was partly due to recruitment taking place during the COVID-19 pandemic. However the inclusion criteria included patients who met the criteria for nr-axSpA in line with BSR guidance[56] and had either responded inadequately to or could not tolerate NSAIDs, and potentially had also responded inadequately to or could not tolerate TNFα inhibitors. This reflects the treatment history

of patients in the UK who would be considered for upadacitinib treatment, as described in Section B.1.3.4.

Likewise, the baseline characteristics of patients included in SELECT-AXIS 2, study 2 were thought to be representative of patients with nr-axSpA who would be considered for upadacitinib treatment in the UK, when clinicians were asked during expert interviews conducted by AbbVie.[4] SELECT-AXIS 2, study 2 recruited nr-axSpA patients who were either bDMARD-experienced or bDMARD-naïve, in line with the patient population who would be eligible for treatment with upadacitinib, as confirmed by clinicians.[4]

The principal limitation of the evidence base is the absence of direct trial-based comparison between upadacitinib, secukinumab and ixekizumab. This has been addressed via an indirect treatment comparison, using the placebo arm that is common to the SELECT-AXIS 2, study 2 and comparator trials to indirectly estimate the comparative effectiveness of upadacitinib compared to IL-17A inhibitors, as described in Section B.3.9.

Table 10. Quality assessment results for SELECT-AXIS 2, study 2

Trial number (acronym)	SELECT-AXIS 2 (NCT04169373)
Was randomisation carried out appropriately?	Yes - the use of interactive response technology (IRT) assigned a randomisation number according to a randomisation schedule which randomised patients in a 1:1 ratio. Randomisation was stratified by MRI and hsCRP screening and bDMARDs exposure.
Was the concealment of treatment allocation adequate?	Yes – blinding of the investigator, study site personal, patients and the sponsor team occurred. To help achieve this identical tablets in appearance of upadacitinib and placebo were used.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – similarity was shown between the baseline characteristics of the two treatment arms (Table 11).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – all personnel involved in the study were blinded to treatment allocation.
Were there any unexpected imbalances in drop-outs between groups?	No – discontinuation was similar between both study arms. At week 14, [redacted] in the upadacitinib and [redacted] in the placebo arm discontinued treatment and [redacted] and [redacted] at week 52 (Appendix J).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No - all outcomes measure were reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No – intention-to-treat analysis was not included in this analysis. For binary endpoints, non-responder imputation in conjunction with multiple imputation (NRI-MI) and for continuous endpoints mixed-effect model repeat measurement (MMRM) was used to account for missing data.
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[59]	

B.3.6 Clinical effectiveness results of the relevant studies

Key points from SELECT-AXIS 2, study 2

- At week 14, significantly more patients in the upadacitinib treatment arm ([redacted]) achieved the primary endpoint of ASAS40 compared to placebo ([redacted]).[55]
- 12 of the 14 multiplicity-controlled secondary endpoints considered reached significance for upadacitinib in comparison to placebo.
- Upadacitinib demonstrated a statistically significantly greater improvement in disease activity, back pain, physical function and quality of life compared to placebo.

- Adverse events were shown to be similar between the upadacitinib, [redacted] and placebo arms, [redacted].
- The SELECT-AXIS 2, study 2 trial demonstrates that upadacitinib improves patient's response and disease symptoms compared to placebo and has a tolerable safety profile.

B.3.6.1 Patient disposition and baseline characteristic

Patient disposition

The SELECT-AXIS 2, study 2 trial randomised [redacted] patients between treatment arms. At the end of week 14, [redacted] of patients in the upadacitinib arm and [redacted] in the placebo arm completed treatment. As seen in Appendix J, similar discontinuation rates occurred between both treatment arms with the most common reason for discontinuation at week 14 being adverse events ([redacted]) in the upadacitinib arm and lack of efficacy in the placebo arm ([redacted]).

At week 52, discontinuation rates in the upadacitinib and placebo arms were [redacted] and [redacted], respectively. Inefficacy was also the most common reason for discontinuation in the placebo arm at week 52 ([redacted]) and "other" was the most commonly reported reason for discontinuation by patients in the upadacitinib arm ([redacted]). Examples of reasons for discontinuation that were defined as "other" included patient moving to a new state/city, patient's inability to get to the appointments due to a busy personal life and site closure.

Baseline characteristics

Table 11 presents the baseline characteristics of patients in SELECT-AXIS 2, study 2, which shows that the patients in each treatment arm were similar at baseline. Slightly more patients were female, [redacted] in the placebo arm and [redacted] in the upadacitinib arm. Most patients were of white race, [redacted] and [redacted] in the placebo and upadacitinib arms,

respectively. The mean age of patients in the placebo arm was [redacted] and [redacted] in the upadacitinib arm.

Across the two treatment arms, mean duration since nr-axSpA diagnosis (placebo: [redacted], upadacitinib: [redacted]) and mean duration since experiencing symptoms of nr-axSpA (placebo: [redacted], upadacitinib: [redacted]) were similar (Appendix J). The time delay between symptom onset and diagnosis is reflective of the delay seen in UK clinical practice,[60] where the NASS reports an average delay of 8.5 years for patients with axial spondyloarthritis.[13]

Endpoint related baseline characteristics, considering the patients' disease severity and symptoms at baseline are presented in Appendix J. These characteristics were also similar between the upadacitinib and placebo arms.

Table 11. SELECT-AXIS 2, study 2 baseline characteristics (FAS)

	Placebo	Upadacitinib
Sex, n (%)		
Female	[redacted]	[redacted]
Male	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
American Indian or Alaska native	[redacted]	[redacted]
Multiple	[redacted]	[redacted]
Age (years)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Age group (Years), n (%)		
< 40	[redacted]	[redacted]
40 - ≤65	[redacted]	[redacted]
≥65	[redacted]	[redacted]
Duration since nr-axSpA symptoms (Years)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Duration since nr-axSpA diagnosis (Years)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Body mass index (kg/m^2)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Body mass index (kg/m^2), n (%)		
< 25	[redacted]	[redacted]
≥25	[redacted]	[redacted]
Region, n (%)		
North America	[redacted]	[redacted]

South/Central America	[redacted]	[redacted]
Western Europe	[redacted]	[redacted]
Eastern Europe	[redacted]	[redacted]
Asia	[redacted]	[redacted]
Other	[redacted]	[redacted]
Tobacco, n (%)		
Current	[redacted]	[redacted]
Former	[redacted]	[redacted]
Never	[redacted]	[redacted]
Alcohol, n (%)		
Current	[redacted]	[redacted]
Former	[redacted]	[redacted]
Never	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Prior bDMARD use, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Reason for prior bDMARD discontinuation, n (%)		
Intolerance	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Lack of efficacy to TNFα inhibitors	[redacted]	[redacted]
Lack of efficacy to IL-17A inhibitors	[redacted]	[redacted]
Source: SELECT-AXIS 2 CSR[55]		

B.3.6.2 Efficacy results

Primary endpoint – ASAS40 at week 14

ASAS40, an improvement in disease activity by 40%, is a robust measure used to assess axSpA treatment response. A statistically significantly increase in the proportion of patients in the upadacitinib group, [redacted] who achieved the primary endpoint of ASAS40 at Week 14 was observed, in comparison to [redacted] in the placebo group. Missing data due to COVID-19 resulted in the use of non-responder imputation incorporating multiple imputation (NRI-MI) producing a placebo adjusted difference of [redacted] (Table 12). From week 2, significantly more patients in the upadacitinib arm achieved ASAS40 in comparison to placebo (**Error! Reference source not found.**).

Table 12. Primary endpoint: ASAS40 response rate at week 14 (NRI-MI, full analysis set)

		Responder		Response rate difference (compared to placebo)		
	N	n (%)	95% CI	Diff (%)	95% CI	P-value
Placebo						
Upadacitinib						
Source: SELECT-AXIS 2 CSR[55]						

Figure 3. ASAS40 response rate up to week 14 in double-blind period (NRI-MI, FAS)

Nominal P ≤ 0.05 at Weeks 2 to 12 and P < 0.0001 at Week 14

Source: SELECT-AXIS 2 CSR[55]

Secondary endpoints

At Week 14, 12 of the 14 multiplicity-controlled secondary endpoints were met for upadacitinib in comparison to placebo (Table 13). This demonstrates that upadacitinib treatment significantly improved outcomes compared to placebo in five key areas of the disease:

- Disease activity: ASDAS (CRP) CFB, ASDAS ID, ASDAS LDA, BASDAI50, ASAS20, ASAS PR
- Functionality: BASFI CFB
- Inflammation: MRI SPARCC score of the SI joint CFB
- Pain: Patient's assessment of total back pain CFB, Patient's assessment of nocturnal back pain CFB
- Quality of life: ASQoL CFB, ASAS HI CFB

Table 13. Summary of multiplicity-controlled secondary efficacy endpoint results at week 14 (FAS)

	N	Responder		Response rate difference (compared to placebo)		
		Within group point estimate	95% CI	Point estimate (95% CI)	P-value	Statistical significance
ASDAS (CRP) CFB						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	< 0.0001	Significant
MRI SPARCC Score (SI joint) CFB						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	< 0.0001	Significant
BASDAI50 response, %						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted])	0.0001	Significant
ASDAS (CRP) ID, %						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	0.0063	Significant
Patient's assessment of total back pain CFB						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	0.0004	Significant
Patient's assessment of nocturnal back pain CFB						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	0.0001	Significant
ASDAS (CRP) LDA, %						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	< 0.0001	Significant
ASAS PR, %						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	0.0035	Significant
BASFI CFB						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	< 0.0001	Significant
ASQoL CFB						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	< 0.0001	Significant
ASAS HI CFB						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	< 0.0001	Significant
ASAS20 Response, %						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	< 0.0001	Significant
$BASMI_{lin}$ CFB						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	0.1781	Not significant
MASES (for patients with baseline enthesitis) CFB						
Placebo	[redacted]	[redacted]	[redacted]		-	
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	0.0193	Not significant

ASAS: Assessment of SpondyloArthritis international Society; ASDA: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMIlin:

Linear Bath Ankylosing Spondylitis Metrology Index; CI: confidence interval; CRP: C-reactive protein; FAS: Full Analysis Set; HI: Health Index; ID: Inactive Disease; LDA: Low Disease Activity; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; MRI: magnetic resonance imaging; PR: partial remission; SI: sacroiliac; SPARCC: Spondyloarthritis Research Consortium of Canada
Source: SELECT-AXIS 2 CSR[55]

Disease activity improvement

ASAS20, ASAS partial remission (PR), ASAS inactive disease (ID) and ASDAS low disease activity (LDA) were achieved by a significantly greater proportion of patients in the upadacitinib arm compared to placebo at week 14 (Table 13). This was also seen from week 2 for ASAS20 response (Appendix J) and from week 4 for ASAS PR response (Appendix J) demonstrating a rapid treatment response to upadacitinib, which was thought to be promising by clinical experts consulted by AbbVie.[4]

At week 14, ASDAS (CRP) score from baseline was significantly improved in the upadacitinib arm versus placebo (Table 13 and Appendix J).

From week 2 to 14, BASDAI50 response was reached by a significantly increased number of patients in the upadacitinib arm (**Error! Reference source not found.**).

Figure 4. BASDAI 50 response rate by visit by week 14 in double-blind period (NRI-MI;FAS)

Functional improvement

In the upadacitinib arm compared to placebo at week 14, BASFI showed significant improvements from baseline, which was established from as early as week 2 (Table 13, Appendix J).

Inflammation improvement

A significantly greater improvement in MRI SPARCC scores for SI joints was demonstrated in the upadacitinib arm compared to placebo at Week 14, which was also seen for the additional secondary endpoint, MRI SPARCC scores of the spine (Appendix J).

Pain improvement

Addressing pain in nr-axSpA patients is an important unmet need, as patients on current advanced therapies still suffer from pain.[23] At week 14, patient's assessment of total back pain and nocturnal back pain from baseline was significantly improved in the upadacitinib arm. Improvements with upadacitinib compared to placebo were demonstrated for total back pain from week 1 or 2 and week 4 onwards for nocturnal back pain (Appendix J).

Quality of life improvement

ASQoL and ASAS HI improvements were significantly greater in the upadacitinib arm in comparison to placebo at week 14 (Table 13).

B.3.7 Subgroup analysis

Subgroup analysis for SELECT-AXIS 2 study 2 considered the following subgroups: age (18- 40, ≥ 40), gender (male and female), race (white vs non-white), weight, BMI (< 25, ≥ 25), geographical region (North America, South/Central America, Eastern Europe, Western Europe, Asia, Other), hsCRP level at screening, prior bDMARD exposure, MRI (SI joints) inflammation at screening, hsCRP/MRI SI joint inflammation at screening, duration since nr-axSpA symptoms and duration since nr-axSpA diagnosis.

The outcomes of the subgroup analysis are presented in Appendix J. All subgroups demonstrated an improved treatment response in ASAS40 in the upadacitinib arm compared to placebo (except for patients with a nr-axSpA diagnosis for 10 years or more), which is in line with results observed for the whole study population (bDMARD-naïve and experienced nr-axSpA patients).

B.3.8 Meta-analysis

The relative effectiveness of upadacitinib and relevant comparators was assessed though a network meta-analysis (Section B.3.9).

B.3.9 Indirect and mixed treatment comparisons

Key points

- No direct trial-based comparisons of upadacitinib to relevant comparators for nr-axSpA were identified. Therefore, two Bayesian NMAs were conducted to compare the efficacy of upadacitinib with ixekizumab and secukinumab.
- The primary NMA is aligned to the patient population considered in this appraisal, nr-axSpA patients presenting with objective signs of inflammation (OSI). A secondary NMA considering the full nr-axSpA population is included for completeness.
- These NMAs demonstrated no significant differences between upadacitinib and IL-17A inhibitors across ASAS40, BASDAI50, BASDAI CFB and BASFI CFB outcomes. Therefore, upadacitinib has comparable efficacy to IL-17A inhibitors for the treatment of active nr-axSpA.
- A comprehensive range of supplementary analyses which present results using alternative trial time points and random or fixed effects models support these findings.
- This confirmed that a cost-comparison is an appropriate method for the economic evaluation of upadacitinib in this appraisal.

Two network meta-analyses (NMA) were conducted to compare the efficacy of upadacitinib to the relevant comparators of IL-17A inhibitors in adult patients with active nr-axSpA that have responded inadequately or have failed to achieve an adequate response with NSAIDs and are either bDMARD-naïve or bDMARD-IR. The primary NMA considered RCTs with patients presenting with OSI and a secondary NMA considered the full nr-axSpA population which included patients with or without objective signs of inflammation (OSI). These are presented as NMA 2 and 4 in

Appendix K. NMAs 1 and 3 consider week 12 endpoints and are also presented in Appendix K, whereas NMAs 2 and 4 utilise week 14 data.

In this submission, the NMA considering the patient population presenting with OSI is considered the primary NMA to align with the patient population of interest as outlined in the anticipated licence for upadacitinib. The NMA considering the full patient population is presented for completeness.

A timepoint of 14 to 16 weeks of treatment was utilised for the primary analysis, as this was reflective of the treatment response assessment timepoints in the SmPCs for these treatments.[1,2] As a result, the timepoints used in the NMA were different between treatments.

The NMA was conducted from a global perspective and so included a wide range of potential comparators. However, this submission will only focus on the results relevant to the decision problem specified in this appraisal, namely the comparison of upadacitinib with the IL-17A inhibitors, secukinumab and ixekizumab.

The following results are described in the submission and the rationale for presenting these results is as follows:

- To align with the primary endpoint of the SELECT-AXIS 2, study 2 trial, a 14 week timepoint for upadacitinib is utilised and reflects the recommended timepoint to assess treatment response.
- Results for ASAS40, BASDAI50, BASDAI CFB and BASFI CFB are presented given that these variables either reflect the primary endpoint of the SELECT-AXIS 2, study 2 trial or are key clinical endpoints recommended by the BSR guidelines to assess nr-axSpA activity.[61]
- The preferred model, either fixed or random effects, is presented and is dependent on model fit.

The results summarised in this submission and in Appendix K demonstrate that upadacitinib has a similar clinical efficacy in comparison to all relevant comparators,

including the IL-17A inhibitors, secukinumab and ixekizumab. Table 14 shows a summary of the NMA inputs.

Table 14. Summary of NMA inputs

	Primary analysis		Scenario analysis	Rationale
Population	Adults with active nr-axSpA and OSI who were NSAID-IR and either bDMARD-naïve or bDMARD-IR		Adults with active nr-axSpA who were NSAID-IR and either bDMARD-naïve or bDMARD-IR	See Section B.3.9.1.3
Comparators	Secukinumab and ixekizumab		Secukinumab and ixekizumab	See Section B.1.1.2
Outcomes	ASAS40, BASDAI50, BASDAI CFB and BASFI CFB		ASAS40, BASDAI50, BASDAI CFB and BASFI CFB	This aligns with NICE scope
Outcome definition	Upadacitinib	14 weeks	14 weeks	This aligns with the endpoint definition of SELECT-AXIS 2, study 2.
	Secukinumab and ixekizumab	16 weeks	16 weeks	Available outcomes are limited to those in the published literature.
NMA modelling methods	Both random and fixed effects models are presented; rationale for primary analysis is documented in Appendix K.			The rationale for primary analysis is documented in Appendix K

B.3.9.1 Methods of the NMA

B.3.9.1.1 Evidence base

B.3.9.1.1.1 Identification and selection of studies

In order to identify relevant studies for inclusion in the NMAs, a systematic literature review (SLR) was conducted (Appendix D).

The initial searches were performed in October 2021. A total of 65 studies were identified with 12 RCTs reported. Only studies that reported relevant week 14 to 16 outcomes were used. Conference abstracts with available subsequent full-text publications were not included in the NMA. Therefore, 13 records contributed data for the 8 RCTs included in the NMA (Appendix J and D) and Figure 5. The SELECT-AXIS 2, study 2 trial, which has not yet been published, and therefore, was not identified in the SLR, was also included in the NMA to inform the upadacitinib arm.

B.3.9.1.1.2 Overview of selected studies

The SELECT-AXIS 2, study 2 trial considers upadacitinib 15 mg QD compared to placebo in patients with active nr-axSpA that are bDMARD-naïve or bDMARD experienced (bDMARD-IR). These populations were pooled for the purpose of the NMAs to align with the population specified in the NICE decision problem and the populations in which secukinumab and ixekizumab are recommended. The percentages of the trial populations what were bDMARD-IR in the SELECT-AXIS 2 study 2 (upadacitinib), COAST-X (ixekizumab) and PREVENT (secukinumab) trials were [redacted], 0% and 11.4% respectively. Given that bDMARD-IR patients have a poorer prognosis than bDMARD-naïve patients, it can be interpreted that the SELECT-AXIS 2, study 2 population represents a harder to treat population and thus, the NMA results for upadacitinib can be considered conservative compared to secukinumab and ixekizumab. Additionally, the higher proportion of bDMARD-IR patients in SELECT-AXIS 2, study 2 was thought to be more representative of UK NHS patients by clinical experts.[4]

Table 15Table 15 presents the 8 RCTs identified in the SLR and SELECT-AXIS 2, study 2, which were included in the NMA as well as their primary and secondary sources if applicable.

Table 15. Overview of the RCTs included from the clinical SLR

Study	Intervention arm(s)	Comparator arm(s)	Study design	bDMARD experience	Primary endpoint	Primary ((secondary) reference(s) used
ABILITY-1 (NCT00939003)	Adalimumab 40 mg Q2W, SC injection	Placebo Q2W, SC injection	Multicentre, DB, randomized, PBO-controlled (12 weeks), phase 3, followed by 144-wk OL phase	bDMARD-naïve	ASAS40 at week 12	Sieper 2013[62] (Corbett 2016[52]; TA719[1])
C-axSpAnd (NCT02552212)	Certolizumab pegol 400 mg SC at weeks 0, 2, and 4 (LD) followed by CZP200 Q2W	Placebo Q2W, SC injection	Multicentre, DB, randomized, PBO-controlled (52 weeks), phase 3, followed by 2-year OL phase	bDMARD-mixed	ASDAS-MI response at week 52	Deodhar 2019[63] (Clinicaltrials.gov[64])
COAST-X (NCT02757352)	Ixekizumab 80 mg Q2W, SC injection	Placebo Q2W, SC injection	Multicentre, DB, randomized, PBO-controlled (52 weeks), phase 3, followed by optional 2-y extension trial (COAST-Y)	bDMARD-naive	ASAS40 at weeks 16 and 52	Deodhar 2020[58] (Deodhar 2021[65]; Poddubnyy 2020[66])
EMBARK (NCT01258738)	Etanercept; 50 mg QW, SC injection	Placebo QW, SC injection	Multicentre, DB, randomized, PBO-controlled (12 weeks), phase 3b, followed by 92-wk OL phase	bDMARD-naïve	ASAS40 at week 12	Dougados 2014[67] (Clinicaltrials.gov[68])
GO-AHEAD (NCT01453725)	Golimumab 50 mg Q4W, SC injection	Placebo Q4W, SC injection	Multicentre, DB, randomized, PBO-controlled (16 weeks), phase 3, followed by 44-wk OL phase	bDMARD-naïve	ASAS20 at week 16	Sieper 2015[69] (van der Heijde 2022[70]; Corbett 2016[52]; TA719[1])
Haibel 2008 (NCT00235105)	Adalimumab 40 mg Q2W, SC injection	Placebo Q2W, SC injection	Multicentre, DB, randomized, PBO-controlled (12 weeks), phase 2/3, followed by 40-wk OL phase	bDMARD-mixed	ASAS40	Haibel 2008[71]

Study	Intervention arm(s)	Comparator arm(s)	Study design	bDMARD experience	Primary endpoint	Primary ((secondary) reference(s) used
PREVENT (NCT02696031)	LD group: Secukinumab 150 mg, SC injection at BL and weeks 1, 2, and 3, then Q4W starting at week 4 Non-LD group: placebo, SC injection at BL and weeks 1, 2, and 3, followed by SEC150 Q4W, SC injection starting at week 4	Placebo, SC injection at BL and weeks 1, 2, and 3, then Q4W starting at week 4	Multicentre, DB, randomized, PBO-controlled (52 weeks), phase 3, followed by OL phase to week 100, with option to continue in additional 2-y extension at week 104	bDMARD-mixed	ASAS40 response at weeks 16 and 52	Deodhar 2021[57] (Marzo-Ortega 2020[72])
RAPID-axSpA (NCT01087762)	Certolizumab pegol 400 mg, SC injection at weeks 0, 2, and 4 (LD) followed by CZP 200 mg Q2W/ CZP 400 mg, SC injection at weeks 0, 2, and 4 (LD) followed by CZP 400	Placebo Q2W, SC injection	Multicentre, DB, randomized, PBO-controlled (24 weeks), phase 3, followed by dose-blind (24 weeks) and 156-wk OL phases	bDMARD-mixed	ASAS20 at week 12	Landewé 2014[73] (Corbett 2016[52]; TA719[1])
SELECT-AXIS-2 (NCT04169373)	Upadacitinib 15 mg oral QD	Placebo QD	Multicentre, DB, randomized, PBO-controlled (52 weeks), phase 3, followed by 52-wk OL phase	bDMARD-mixed	ASAS40 at week 14	Data on file[55]

ASAS: Assessment of SpondyloArthritis international Society; ASAS20/40: improvement of ≥20%/40% and an absolute improvement of at least 10 units on a 0–100 scale in ≥3 of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last two questions of BASDAI); ASDAS: Ankylosing Spondylitis Disease Activity Score; bDMARD: biologic disease-modifying anti-rheumatic drug; CZP: certolizumab pegol; DB: double blind; LD: loading dose; NSAID=nonsteroidal anti-inflammatory drug; OL=open label; OLE: open-label extension; PBO: placebo; QD: once per day; QW: once per week; Q2/4W: every 2/4 weeks; SC: subcutaneous; SEC: secukinumab.

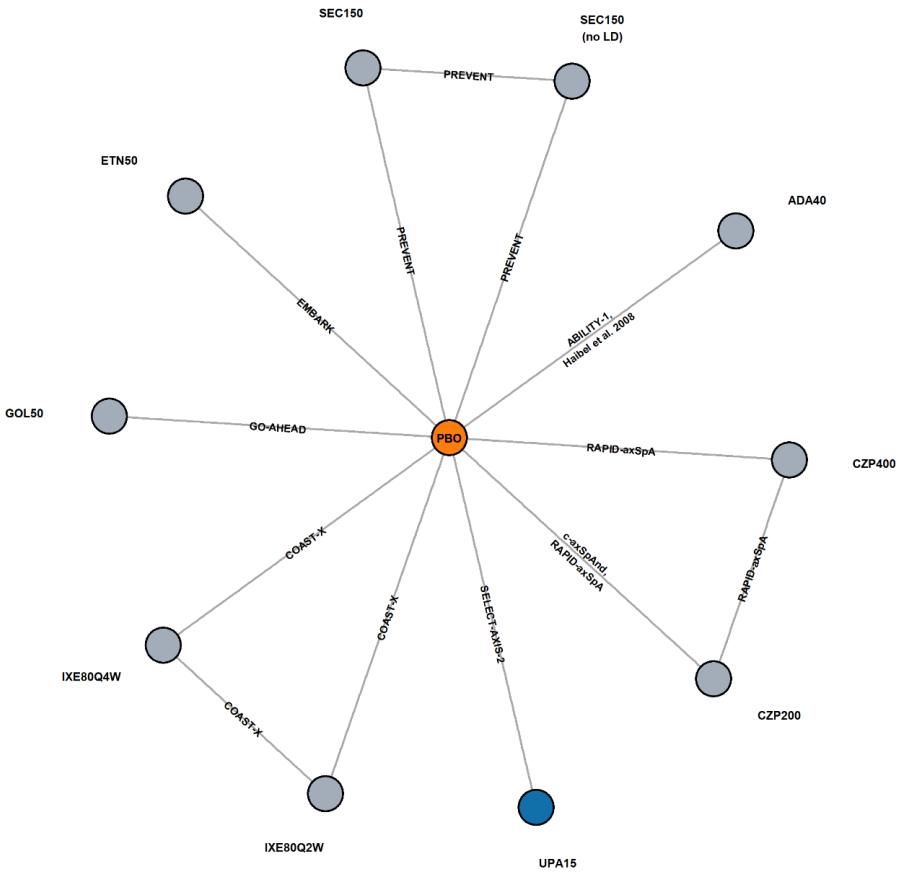
B.3.9.1.2 NMA networks

The relevant trials, the treatment and dosing schedules considered and a summary of the endpoints of interest available for inclusion in the NMAs are summarised in Appendix K, Section 5.2.

The network diagram shows the complete treatment network of the RCTs included in the NMAs (Figure 5). All available treatments for nr-axSpA at the time of this analysis are included based on the criteria described in Section B.3.9.1.3.

Within the network diagram the nodes represent a treatment regimen, and the lines show the direct comparisons between the nodes. Along each line, the studies contributing to each comparison are shown. In Appendix K, Sub-appendix C, network diagrams for each outcome are presented. Please note, only the outcomes of the comparisons between upadacitinib, secukinumab and ixekizumab are relevant to this submission.

Figure 5. Complete treatment network of RCTs among nr-axSpA patients



ADA40: adalimumab 40 mg Q2W; CZP200/400: certolizumab pegol 200/400 mg loading dose at weeks 0, 2 and 4, then MD Q2/4W; ETN50: etanercept 50 mg QW; GOL50: golimumab 50 mg Q4W; IXE80Q2W/Q4W: ixekizumab 80 mg Q2W/Q4W; UPA15: upadacitinib 15 mg QD; SEC150: secukinumab 150 mg MD Q4W.

B.3.9.1.3 Methods and outcomes of included studies

Population

Studies included in the NMA were adults with active nr-axSpA who were NSAID-IR and either bDMARD-naïve or bDMARD-IR. Full PICOS criteria is found in Appendix K. Baseline characteristics were gathered and compared across the trials where heterogeneity could be identified (Appendix K, Section 4.5.2). Baseline risk adjustments are shown in Appendix K, Section 4.5.6.

While SELECT-AXIS 2, study 2 and PREVENT trial for upadacitinib and secukinumab, respectively, recruited mixed bDMARD-naïve or bDMARD-IR patient populations, the COAST-X trial for ixekizumab, recruited an exclusively bDMARD-naïve patient population[58].[57] Due to the limitations in the data available from the comparator studies, it was not possible to conduct NMAs in the bDMARD-naïve or bDMARD-IR populations separately. As patients who have previously failed one bDMARD are more likely to respond inadequately to a second bDMARD,[37] it is believed that including a greater proportion of bDMARD-IR patients in the upadacitinib arm of the NMA is a conservative approach when considering the relative efficacy between these treatment arms.

Timepoint

Outcomes were assessed at either week 14 or 16. For SELECT-AXIS 2, study 2, the primary endpoint at week 14 was prioritised with week 12 outcomes included in a scenario analyses (NMA 1 and 3 within Appendix K). As secukinumab and ixekizumab were assessed at week 16 during the PREVENT and COAST-X trials, it is possible that patients treated for 16 weeks would have a slightly greater treatment response to those treated for 14 weeks, as they had a longer period for response. However, it was felt by the experts during the interviews conducted by AbbVie that this approach is conservative when assessing the relative efficacy of upadacitinib to these treatments due to the possibility of bias against upadacitinib as it is assessed at an earlier timepoint, therefore, a lower treatment response might be expected.[4]

Missing data

The RCTs included in the NMAs used similar strategies to impute missing outcomes (Appendix K, Section 5.2.2.3). Non-responder imputation (NRI) was used for the majority of binary outcomes and last observation carried forward (LOCF) for continuous outcomes. However, the COAST-X and PREVENT trials for IL-17A inhibitors used mixed-effect model repeated measures (MMRM) for continuous

outcomes and the SELECT-AXIS 2, study 2 trial utilised NRI with multiple imputation (NRI-MI) to account for additional missing data due to COVID-19 infection.

B.3.9.1.4 Methods of analysis and presentation of results

For each feasible network, NMAs were conducted in a Generalised Linear Model (GLM) framework using Bayesian Markov Chain Monte Carlo (MCMC) simulations and three chains with 100,000 runs each, with a burn-in that was half of the convergence sequence (set size of 10,000).[74,75] Convergence was assessed with the Brooks-Gelman-Rubin method using the Potential Scale Reduction Factor (PSRF). The PSRF should gradually shrink to one with increasing numbers of iterations; a value of <1.05 was used to indicate convergence.[76]

A Bayesian NMA requires the selection of a likelihood distribution that reflects the nature of the data (e.g., continuous, rate, categorical) and the sampling process that generated them (e.g., normal, binomial, Poisson, multinomial), as well as a transformation (link function) that maps the data into a continuous measure between plus and minus infinity (e.g., identity, logit, log). Per the NICE Decision Support Unit Technical Support Document 2 (DSU TSD2), binary outcomes were modelled with a binomial likelihood and logit link function, while continuous outcomes were modelled with a normal likelihood and identity link function.[74,77]

By default, RCT-specific baselines μ_i, shown in the equation below as representing the log odds of the outcome in the placebo arm, were modelled as independent, such that an unrelated model parameter were specified for each one.

$$logit(p_{ik}) = \mu_i + \delta_{i,1k}$$

However, in networks with one or more placebo arms having a value of zero, an exchangeable baseline assumption was used to aid parameter estimation and numerical stability/convergence.[77] For all networks, both FE and RE models were tested.

As detailed in the NICE DSU TSD2, vague or flat prior distributions were given to the parameters to be estimated by default.[74,77] For parameters assumed to be specified on a continuous scale, namely the relative treatment effects d, RCT-specific baselines

μ, and baseline adjustment regression term B (for models with baseline risk adjustment), a normal (0, 1002) prior distribution was used. For the between-study standard deviation (SD) (for RE models), a uniform (0, 5) prior distribution was used.

Posterior distributions were visually inspected for spikes and unwanted peculiarities. For the between-study SD, posterior distributions were inspected for adequate posterior updating. In cases where the posterior distribution of SD appeared to include implausibly high values, such as when all treatments are informed only by a single trial or model convergence could not be achieved, a gamma (0.001, 0.001) prior distribution on the precision that gives a low prior weight to unfeasibly large SDs on the logit scale was tested. [77,78]

Model output

Relative treatment effects were modelled as log odds for binary outcomes and mean differences for continuous outcomes in the NMA. From the log odds, odds ratios (ORs) were derived. For both binary and continuous outcomes, given information on the absolute effect of a reference placebo treatment, absolute treatment outcomes which are the probabilities for binary and CFBs for continuous were also predicted.[74] All posterior distributions (including those for ORs and predicted absolute outcomes) were summarised by their medians and 95% CrIs.

B.3.9.1.5 Risk of bias

The trials included in the NMA were quality assessed in line with NICE guidelines (Appendix D).

B.3.9.2 Results

The NMAs show upadacitinib to be statistically significantly better than placebo for all key outcomes, ASAS40, BASDAI50, BASDAI CFB and BASFI CFB. Upadacitinib also demonstrated similar efficacy to the relevant comparators, secukinumab and ixekizumab for these outcomes.

B.3.9.2.1 ASAS40

For ASAS40, the primary endpoint of SELECT-AXIS 2, study 2, the fixed effects (FE) model was preferred when considering the OSI only population. The alternative

gamma prior distribution for SD was tested as each network contained only one study per treatment arm. In the FEA model for the ASAS40 outcome convergence did not occur. The RE models posterior SDs density plots provided unrealistically high estimates of between-study heterogeneity, and resultantly the dataset was concluded too sparse to inform the RE model (Appendix K, Section 5.3.2).

Considering ASAS40 in the full population, the FE model was also preferred. This was due to the fixed effects model with placebo-adjustment (FEA) model not converging and the random effects (RE) model's posterior SDs density plots providing unrealistically high estimates of between-study heterogeneity. Therefore, the dataset was concluded too sparse to inform the RE model (Appendix K, Section 5.3.2).

For the binary outcome of ASAS40, upadacitinib was statistically significantly better than placebo and was found to be statistically similar to secukinumab and ixekizumab in both the OSI population and full study population (Table 16). The credible interval for the OSI population for ixekizumab is large as the data informing this comparison is limited, however, the results align with the full population analysis, which was informed by more trial data.

Table 16. Odds ratios of ASAS40 for upadacitinib versus comparators – Week 14

	OSI population			Full Population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC150 no LD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks; SEC150 (no LD): secukinumab 150mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; OSI: objective signs of inflammation;

B.3.9.2.2 BASDAI50

For BASDAI50, in the OSI population and full population, the FE models were the preferred models. Convergence was not seen with the FEA models and the RE models' posterior SDs density plots resulted in unrealistically high estimates of

between-study heterogeneity of the gamma prior distribution. As a result, in the RE models, the dataset was determined too sparse (Appendix K, Section 5.3.4).

For the binary outcome of BASDAI50, upadacitinib was determined statistically significantly better than placebo and was found to be statistically similar to secukinumab and ixekizumab in both the OSI population and full study population (Table 17). The credible interval for the OSI population for ixekizumab is large due to the limited data available to inform this comparison, however the results align with the full population NMA, which was informed by more trial data.

Table 17. Odds ratios of BASDAI50 for upadacitinib versus comparators – Week 14

	OSI population			Full population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150 no LD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks SEC150 (no LD): secukinumab 150/300 mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; OSI: objective signs of inflammation;

B.3.3.2.3 BASDAI CFB

For the OSI only population, FEA did not show convergence and RE models posterior SDs density plots provided unrealistic high estimates of between-study heterogeneity of the gamma prior distribution. Therefore, the FE model was favoured in this population (Appendix K, Section 5.3.5).

In analysis of BASDAI CFB in the full population, the dataset for the RE model was considered too sparse to inform the model. This is because unrealistically high estimates of between-study heterogeneity of the uniform (0, 5) prior distribution were found from density plots of the RE models posterior SDs. The FEA model did not converge unlike the other models considered, therefore the FE was preferred (Appendix K, Section 5.3.5).

For BASDAI CFB, a continuous outcome, upadacitinib was statistically significantly better in comparison to placebo and similar to secukinumab and ixekizumab in both the OSI population and full study population (Table 18).

Table 18. Relative effect of BASDAI CFB for upadacitinib versus comparators – Week 14

	OSI population			Full population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150 no LD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks; SEC150(no LD): secukinumab 150 mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; OSI: objective signs of inflammation;

B.3.9.2.4 BASFI CFB

For the OSI only population, the FE model was selected as FEA did not show convergence and inadequate posterior updating of the gamma prior distribution in the density plots of the RE models posterior SDs occurred (Appendix K, Section 5.3.6).

The FE model was preferred for BASFI CFB analysis in the full population as FEA did not converge and the density plots of the RE model's posterior SDs were found to have unrealistically high estimates of between-study heterogeneity of the uniform (0, 5) prior distribution meaning the RE dataset was too sparse to inform the model (Appendix K, Section 5.3.6).

The continuous outcome of BASFI CFB showed upadacitinib to be statistically significantly better in comparison to placebo and similar to secukinumab and ixekizumab in both the OSI population and full study population (Table 19).

Table 19. Relative effect of BASFI CFB for upadacitinib versus comparators – Week 14

	OSI population			Full population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150 no LD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks; SEC150 (no LD): secukinumab 150 mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; OSI: objective signs of inflammation;

B.3.9.3 Results of the assessment of heterogeneity

The relevant studies and patient characteristics of the RCTs included in the NMA network were reviewed in order to determine their comparability and potential sources of cross-study heterogeneity. The NMAs were conducted from a global perspective, and so a broad selection of therapies were included. As these studies are linked in the NMA via the common placebo arm, all studies included in the NMA network were assessed for heterogeneity as heterogeneity between these studies would have impacted this common arm.

From published clinical research,[79-83] baseline characteristics were identified *a priori* to be potential treatment effect modifiers or prognostic factors. These baseline characteristics include age, sex, duration of disease, CRP levels (mg/L, some may be high sensitivity), elevated CRP levels (CRP+, yes/no), human leukocyte antigen B27 (HLA-B27) positive (yes/no), functional status (BASFI scores), disease severity (BASDAI scores), total back pain scores, MRI sacroiliitis positive (MRI+, yes/no), Spondyloarthritis Research Consortium of Canada (SPARCC) MRI sacroiliac joint score (range 0-72) and prior and concomitant medication use. When considering these potential treatment effect modifiers or prognostic factors, across all trials included in the NMA, the following areas of potential heterogeneity were identified:

- In terms of age, the EMBARK and GO-AHEAD trials had a younger patient population and SELECT-AXIS 2 older patients.

- Duration of disease was reported as years from diagnosis in the majority of RCTs, however duration of disease from initial symptoms was reported in EMBARK, Haibel et al. 2008, and RAPID-axSpA.

- The duration from symptoms was overall greater than duration from diagnosis except from in the EMBARK trial where duration from symptoms was similar to duration from diagnosis in the other RCTs.

- c-axSpAnd and GO-AHEAD RCTs were determined to have an increased proportion of HLA-B27 positive and a lower proportion was seen in SELECT-AXIS 2.

- ABILITY-1, c-AxSpAnd and EMBARK RCTs had 95% CIs that excluded the mean CRP level of 10.9 mg/L. Variation was detected in elevated CRP levels due to the differing threshold used in the RCTs. Upper limit of normal (ULN) was used in ABILITY-1, c-axSpAnd, GO-AHEAD and RAPID-axSpA, greater than 3 mg/L in the EMBARK trial and greater than 5 mg/L for COAST-X, PREVENT and SELECT-AXIS 2. Elevated CRP was not reported in Haibel et al. 2008.

- The mean baseline BASFI score of the included RCTs was 5.4, EMBARK, COAST-X, PREVENT and SELECT-AXIS 2 had 95% CIs that excluded this mean.

- EMBARK, COAST-X, and SELECT-AXIS 2 had 95% CIs that excluded the mean baseline total back pain score of 6.9. Total back pain score was not reported by Haibel et al. 2008 and RAPID-axSpA.

- Considering, prior biologic use, concomitant NSAID use, concomitant csDMARD use and concomitant glucocorticoid use these characteristics are generally similar between RCTs. In the SELECT-AXIS 2 trial a higher proportion of bDMARD-exposed patients were detected.

- ASAS40 and ASASPR baseline risks in both the OSI only population and full population showed significant variation across the RCTs included (Appendix K, Section 5.2.2.5 and Sub-appendix A).

- Considering the SPARCC MRI sacroiliac joint score, GO-AHEAD, PREVENT and SELECT-AXIS 2 had 95% CIs that excluded the mean of 6.2. In the PREVENT trial, its lower than mean value could be attributed to by a lack of clarity if this measure was utilised. SPARCC MRI sacroiliac joint score was not reported for Haibel et al. 2008 and RAPID-axSpA.

Overall, some but minimal cross-study heterogeneity of baseline patient characteristics among the included RCTs was detected, due to similarities between RCTs. The demographic characteristics of age and sex were similar as well as most disease characteristics, with the exception of MRI sacroiliitis positive and elevated positive CRP levels. Baseline clinical scores of BASDAI, BASFI, and Total Back Pain scores also showed similarities. For further detail refer to Appendix K, Section 5.2.2.4 and Sub-appendix B.

Additionally, an assessment of the mean baseline placebo effects of the RCT included was conducted. To address any discernible heterogeneity across the RCTs, adjustment of baseline risk as a proxy for both measured and unmeasured patient- and study-level characteristics that can collectively influence a patient's response to treatment was utilised instead of adjusting for individual characteristics.[84-88] See Appendix K, Section B.4.5.6 for more detail.

B.3.9.4 Uncertainties in the indirect and mixed treatment comparisons

The assumptions underlying the NMA can be considered a limitation. Careful consideration of the network connectivity, homogeneity and transitivity or consistency must be actioned to avoid their violation and jeopardising the conclusions of the NMA. A key limitation of the NMA was data sparsity which resulted in the consistency assumption only being assessed in a subset of endpoints. The conclusions of the NMA were subject to the method quality, reporting biases and selected eligibility criteria of the RCTs included. Between-study heterogeneity in the full population NMA may have

been a result of the inclusion of nr-axSpA patients with and without OSI, however it was highlighted that a high proportion of those in the full population have OSI.

The selection of FE as the preferred model was largely due to data sparsity and a lack of convergence or insignificant regression coefficients with RE and risk-adjusted models. In general, despite using the minimally informative gamma prior distribution for sd where needed, none of the RE models exhibited face validity. Given that the majority of treatments were informed by a single study, poor performance of RE models (which assume an underlying distribution of effect for a treatment as opposed to a singular effect for a treatment) is not unexpected. Data sparsity was also an issue in the appraisals for ixekizumab[2] and golimumab for nr-axSpA.[41] Resultantly, the results using FE could have inflated precision. See Appendix K for additional detail.

B.3.9.5 Conclusions of the ITC

The NMAs considering the OSI and full populations at week 14 determined upadacitinib to be statistically significantly better in comparison to placebo for all key outcomes of ASAS40, BASDAI50, BASDAI CFB and BASFI CFB, which aligns with results observed in the SELECT-AXIS2, study 2 trial. Additionally, this analysis concluded upadacitinib to be similar to the relevant comparators IL-17A inhibitors, secukinumab and ixekizumab for both the OSI and full populations in all outcomes.

Overall, in terms of efficacy upadacitinib is comparable to the IL-17A inhibitors, secukinumab and ixekizumab in both the OSI population and full nr-axSpA population. Therefore, upadacitinib for nr-axSpA patients meets the NICE cost-comparison route criteria (Section B.1).

B.3.10 Adverse reactions

Upadacitinib was well tolerated during SELECT-AXIS2, study 2, with no new safety concerns identified when compared to previous upadacitinib studies. A similar proportion of patients in both the placebo and upadacitinib arms experienced adverse events (AEs), including treatment-related AEs (TRAEs) and serious AEs (SAEs) (Table 20). During expert interviews conducted by AbbVie, clinicians commented that the safety profile was aligned to that observed with current treatments for nr-axSpA, including IL-17A inhibitors, and did not raise any new safety concerns.[4]

In SELECT-AXIS 2, study 2, [redacted] of patients treated with upadacitinib experienced AEs and [redacted] experienced serious adverse events (SAEs) compared to [redacted] and [redacted] of patients in the placebo arm, respectively.

The proportion of treatment-emergent adverse events (TEAEs) observed was similar between the placebo and upadacitinib arms in SELECT-AXIS 2, study 2 at week 14, [redacted] and [redacted], respectively. In terms of SAEs, severe AEs and TEAE leading to discontinuation of study drug at week 14, the proportion of patients experiencing these adverse reactions was also similar in the upadacitinib arm compared to placebo (Table 20).

Table 20. Overview of treatment-emergent adverse events and all death - By week 14 double-blind period (safety analysis set)

	Placebo (N=157) n (%)	Upadacitinib (N=156) n (%)	Upadacitinib - Placebo (95% CI)
AE	[redacted]	[redacted]	[redacted]
AE with reasonable possibility of being related to study drug	[redacted]	[redacted]	[redacted]
Severe AE	[redacted]	[redacted]	[redacted]
Serious adverse event	[redacted]	[redacted]	[redacted]
AE leading to discontinuation of study drug	[redacted]	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]
COVID-19 related AE	[redacted]	[redacted]	[redacted]
All deaths	[redacted]	[redacted]	[redacted]
AE: adverse event;			

At week 52, SAEs and COVID-19 related TEAEs were similar between both study arms. TEAEs leading to the discontinuation of study drug, severe AEs and exposure-adjusted event rates (EAERs) for TEAEs were detected in a larger proportion of patients treated with upadacitinib in comparison to placebo (Appendix J).

Infections including oral herpes, nasopharyngitis and upper respiratory tract infection were seen more frequently in the placebo arm at week 14. Headache, nausea, abdominal pain, diarrhoea, and neutropenia were found to occur more often in the upadacitinib arm (Table 21**Error! Reference source not found.**).

Table 21. Treatment-Emergent Adverse Events Reported in > 2% of Subjects in any Treatment Group by Decreasing Frequency in Upadacitinib Group – By Week 14 (Safety Analysis Set)

MedDRA 24.0 Preferred Term	Placebo (N = 157) n (%)	Upadacitinib (N = 156) n (%)
Any adverse event	[redacted]	[redacted]
Headache	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Oral Herpes	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]

A similarly low frequency was observed between both treatment arms for new onset extra-articular manifestations. There was [redacted] new onset of exacerbation of IBD in the upadacitinib or placebo arm up to week 52. At week 14, [redacted] uveitis event occurred in the upadacitinib arm in a patient with a history of uveitis. By week 52, [redacted] uveitis events occurred, [redacted] of which were in a single patient without a history of uveitis and [redacted] in a patient with a prior history of uveitis. All [redacted] events occurred in [redacted] patients in the upadacitinib arm. Venous thromboembolic events (VTE), major adverse cardiac events (MACE) or malignancy were [redacted] in any patients up to week 52 in the upadacitinib arm (Appendix J).

The safety profile of upadacitinib observed during SELECT-AXIS 2, study 2, was consistent with that observed during SELECT-AXIS 1, the trial considering the use of upadacitinib for patients with AS,[48] and that observed with ixekizumab and secukinumab in patients with nr-axSpA[57,58] as presented in Table 22. For example, [redacted] of nr-axSpA patients treated with upadacitinib experienced an AE during the first 14 weeks of SELECT-AXIS 2, study 2, which was similar to the rate of AEs observed with secukinumab and ixekizumab treatment in the first 20 and 16 weeks of the PREVENT and COAST-X trials (61.2%, and 66% respectively).

Likewise, the rate of discontinuation in the SELECT-AXIS 2, study 2 trial was [redacted] for all patients with [redacted], discontinuing due to adverse events. The rate of discontinuation

observed in the trials for secukinumab and ixekizumab over similar timeframes were similar to those observed for upadacitinib in nr-axSpA patients, (9%, 1% and [redacted], respectively), with 1%, 0% and [redacted] of patients, respectively, discontinuing due to adverse events.

The COAST-X trial for ixekizumab[58] and the PREVENT trial for secukinumab,[57] deemed both treatments safe for nr-axSpA patients; adverse events were consistent with those already observed and no new safety concerns were identified during these trials.[19,89] Likewise, no new safety concerns were identified during SELECT-AXIS 2, study 2.

Table 22. A comparison of the safety outcomes across nr-axSpA trials

	SELECT-AXIS 2, study 2[55]		COAST-X[58]		PREVENT[57]	
Week	14		16		20	
Population	nr-axSpA		nr-axSpA		nr-axSpA	
Treatment	Upadacitinib	Placebo	Ixekizumab	Placebo	Secukinumab	Placebo
n	156	157	96	104	369	186
Any AE	[redacted]	[redacted]	63 (66)	60 (57)	226 (61)	101 (54)
SAEs	[redacted]	[redacted]	1 (1)	1 (1)	6 (2)	5 (3)
AEs leading to discontinuation	[redacted]	[redacted]	1 (1)	2 (2)	3 (1)	3 (2)
Death	[redacted]	[redacted]	0	0	0	0
Discontinuation	[redacted]	[redacted]	1 (1)	7 (7)	17 (9)*	11 (6)*
Discontinuation due to AEs	[redacted]	[redacted]	0 (0)	2 (2)	3 (1)	3 (2)

AEs: adverse events; AS: ankylosing spondyloarthritis; nr-axSpA: non-radiographic axial spondyloarthritis; SAEs: serious adverse events;

*Data given for week 24

B. 3.10.1 Long term safety profile of Upadacitinib

Upadacitinib is currently approved in RA, Psoriatic arthritis, AS (15mg) and atopic dermatitis (AD) (15mg and 30mg) in major markets worldwide, including the EU and Japan.

The safety profile of upadacitinib can be assumed comparable to other IL-17A inhibitors used for nr-axSpA patients (Table 22). Over 104 weeks, SELECT-AXIS 1, a trial investigating the efficacy and safety of upadacitinib in an AS population, determined that a similar number of patients in the placebo and upadacitinib groups experienced AEs.[90,91] SELECT-AXIS 2, study 2 has provided similar safety results over a shorter time horizon. Therefore, due to the parallels between AS and nr-axSpA, it can be assumed that treatment with upadacitinib for nr-axSpA patients will achieve a comparable longer term safety profile to that of AS. This is further supported by upadacitinib use in AS, RA and psoriatic arthritis over a 4.5 year time period where it showed no new safety signals.[91]

B.3.11 Conclusions about comparable health benefits and safety

Upadacitinib is proposed as the inaugural JAK inhibitor for patients with active nr-axSpA with OSI who have responded inadequately to NSAIDs and who are not suitable for treatment with or whose condition is not controlled well enough by TNFα inhibitors. In comparison to ixekizumab and secukinumab, the oral, once daily administration route of upadacitinib is both beneficial to healthcare professionals and to patients due to its more convenient nature and provides relief for needle-phobic patients. Upadacitinib, as a JAK inhibitor, presents an alternative mechanism of action, therefore, offering an additional treatment option for nr-axSpA patients and healthcare professionals.

SELECT-AXIS 2, study 2 was a phase 3 multicentre, randomised, double-blind, placebo-controlled, two-period, parallel-group trial, which considered the efficacy, safety and tolerability of upadacitinib compared to placebo for the treatment of nr-axSpA patients who were either bDMARD-IR or bDMARD-naive. The trial was thought to be representative of routine clinical practice in the UK as the inclusion criteria aligns with BSR guidelines,[56] and reflects the current clinical pathway of nr-axSpA patients

in the UK: patients who have responded inadequately to or are not suitable for NSAIDs, and potentially had also responded inadequately to or were unsuitable for TNFα inhibitors. This was also confirmed by clinical experts from the UK who highlighted that the inclusion criteria and baseline characteristics of the patients aligned with current clinical practice.[4]

The SELECT-AXIS 2, study 2 trial shows upadacitinib to have a high degree of efficacy for the treatment of nr-axSpA patients (Section B.3.6.2.6). In comparison to the placebo arm ([redacted]), a significantly higher proportion of patients in the upadacitinib arm achieved the primary endpoint of ASAS40 at week 14 ([redacted]) (Table 12). This trend commenced from week 2 onwards showing a rapid treatment response to upadactninb.[55]

Overall, 12 of the 14 multiplicity-controlled secondary endpoints considered reached significance for upadacitinib versus placebo at week 14 (Table 13).[55] Upadacitinib showed statistically significantly greater improvements in disease activity, back pain, physical function and quality of life in comparison to placebo.

The IL-17A inhibitors, secukinumab and ixekizumab are considered relevant comparators for upadacitinib. UK clinical experts stated that upadacitinib would be used as an alternative treatment to IL-17A inhibitors in clinical practice. Due to the lack of trial-based comparisons of upadacitinib and IL-17A inhibitors, two Bayesian NMAs were used to compare the effectiveness of upadacitinib to its relevant comparators (Section B.3.9).

Considering ASAS40, BASDAI50, BASDAI CFB and BASFI CFB, upadacitinib showed no significant differences in comparison to IL-17A inhibitors, secukinumab and ixekizumab in both NMAs. This demonstrates that upadacitinib has a comparable efficacy to IL-17A inhibitors.

The SELECT-AXIS 2, study 2 trial demonstrated upadacitinib to be well tolerated by nr-axSpA patients with no new safety concerns detected. A similar proportion of nr-axSpA patients in the placebo and upadacitinib arms experienced AEs ([redacted] and [redacted]), SAEs ([redacted] and [redacted]) and TEAEs ([redacted] and [redacted]) at week 14. In term of AEs leading to discontinuation, this occurred in [redacted] of patients in the placebo arm

compared to [redacted] in the upadacitinib arm. Additionally, no deaths were reported (Section B.3.10).

Overall, when considering the patient population addressed in this submission: patients with active nr-axSpA with objective OSI who have responded inadequately to NSAIDs and who are not suitable for treatment with or whose condition is not controlled well enough by tumour necrosis factor TNFα inhibitors, upadacitinib demonstrates comparable health benefits in relation to the current comparators in the NICE recommended treatment pathway.

B.3.12 Ongoing studies

Period 2 of the SELECT-AXIS 2 trial is currently ongoing. There are no other ongoing studies for upadacitinib for the treatment of nr-axSpA patients.

B.4 Cost-comparison analysis

As presented in the indirect treatment comparison provided in Section B.3.9, upadacitinib demonstrates comparable clinical efficacy compared to secukinumab and ixekizumab in each of the outcomes of interest within this appraisal; ASAS40, BASDAI50, BASDAI CFB and BASFI CFB. Therefore, a cost-comparison analysis is deemed appropriate as all efficacy and safety outcomes are likely to be comparable. The cost-comparison analysis undertaken considers the drug acquisition and administration costs, alongside resource utilisation over a five year period, with total costs estimated as a function of time on treatment.

As previously described in Section B.1.1, upadacitinib is an alternative treatment to secukinumab and ixekizumab. Therefore, the cost-comparison analysis presented focuses on the comparison of costs associated with ixekizumab, secukinumab and upadacitinib.

B.4.1 Changes in service provision and management

nr-axSpA is a chronic condition with no known cure that results in pain and a reduced QoL for patients with this condition. There is currently a high unmet need for treatments

that offer alternative modes of administration and mechanisms of action to the IL-17A inhibitors that are currently available.

As an oral treatment, upadacitinib offers an alternative mode of administration to the IL-17A inhibitors, which are administered by subcutaneous injection. The introduction of a once daily oral formulation would provide a more convenient option to nr-axSpA patients as detailed in Section B.1.3.5. Likewise, as the first JAK inhibitor licenced for the treatment of nr-axSpA, upadacitinib offers an alternative mechanism of action, giving clinicians and patients another therapeutic option.

The main cost component associated with all treatments is the underlying drug acquisition cost. Ixekizumab and secukinumab, are administered via subcutaneous injection and are therefore associated with different administration costs compared to upadacitinib. The monitoring costs for all three treatments are expected to be identical, due to the similar safety and efficacy profiles of the treatments (Section B.3.9 and B.3.10), and therefore, it is anticipated that there will be no increase in service provision or management and no additional health care infrastructure will be required for the introduction of upadacitinib.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

The cost-comparison analysis presented estimates the costs associated with treatment and monitoring over a five-year time horizon, with total costs disaggregated by individual year. As secukinumab and ixekizumab are administered via subcutaneous injection, their administration is associated with an initial training cost, which is not required for upadacitinib as this is an oral treatment. However, the long-term administration costs are considered similar for all treatments included in this analysis. Feedback from clinical experts from interviews conducted by AbbVie supported the assumption that discontinuation rates and monitoring frequency are similar across all treatments. Expert opinion elicited from a health economist also agreed that the key driver of total costs is expected to be the differences in drug acquisition costs.

Given the similarity in the treatment pathways and the low discontinuation rates associated with treatment, a five-year time horizon has been considered appropriate to reflect any important differences between the treatments being compared. Outcomes over a one-year period are also presented in the base case analysis (Table 26). Further scenario analysis has been presented comparing outcomes over an extended ten-year time horizon, consistent with the approach adopted in TA497 (golimumab for treating nr-axSpA).[40] The adopted five-year time horizon in the base case is considered more than adequate to reflect materially important differences between the technologies being compared.

Given the similarity between upadacitinib, ixekizumab and secukinumab, as demonstrated in Section B.3.9 and Table 22, and in line with the current consensus that discontinuation rates are similar across treatments for nr-axSpA, a discontinuation rate of 6% per annum has been utilised in the analysis. This is consistent with the approach taken in recent NICE technology appraisals for nr-axSpA and considered appropriate by external review groups in NICE (TA383[29] and TA719[1]) and by clinical experts whose opinion was sought during interviews (Section B.4.2.6).

Once a patient discontinues a treatment, it is assumed that they will not incur any further costs for the purpose of this analysis. Discontinuation rates have been applied at 3-monthly intervals, in line with cycle lengths used in recent NICE technology appraisals for nr-axSpA, TA383,[29] TA718[2] and TA719.[1]

B.4.2.2 Intervention and comparators' acquisition costs

Drug acquisition costs and details of relevant patient access schemes (PAS) for upadacitinib are presented in Table 23. The drug acquisition costs of ixekizumab and secukinumab are also included. However, as PAS's are not published for these therapies, no discounting of their acquisition costs could be conducted in this analysis. All drug acquisition costs are sourced from the BNF.[92] Treatment frequencies and doses are assumed to be administered at licensed doses to ensure that costs represent clinically feasible doses.

Table 23. Acquisition costs of the intervention and comparator technologies

	Upadacitinib	Ixekizumab	Secukinumab
Method of administration	Oral	Subcutaneous injection	Subcutaneous injection
Provider company	AbbVie Ltd	Eli Lilly and Company Ltd	Novartis Pharmaceuticals UK Ltd
Pack description	Upadacitinib (as Upadacitinib hemihydrate) 15 mg - tablet (POM)	Taltz 80mg/1ml solution for injection pre-filled pens	Secukinumab 150 mg per 1 ml - pre-filled disposable injection (POM)
Pack size (no. of units)	28	1	2
Acquisition cost per pack (£)	£805.56	£1,125.00	£1,218.78
Acquisition cost per unit (£)	£28.77	£1,125.00	£609.39
Source	BNF[92]	BNF[92]	BNF[92]
Summary of dose and dose frequency			
Recommended dose	15 mg once daily, for treatment interruption due to side-effects—consult product literature.	Initially 160 mg for 1 dose, then maintenance 80 mg every 4 weeks, consider discontinuation of treatment if no response after 16–20 weeks.	150 mg every week for 5 doses, then maintenance 150 mg every month, dose may be increased to 300 mg according to clinical response. Review treatment if no response within 16 weeks of initial dose. [A]

Dose frequency	Once daily	160 mg for 1 dose, then maintenance 80mg every 4 weeks.	One 150 mg every week for 5 doses, then maintenance 150 mg every month
Dose size	15mg	80mg	150mg
Number of dose in initial 3 months	91.31	4	7
Number of doses in subsequent 3-month periods	91.31	3.26	3
Source	BNF[92]	BNF[92]	BNF[92]
Summary of costs			
Cost per dose (£)	£28.77	£1,125.00	£609.39
Description of PAS (if applicable)	[redacted]	Ixekizumab is offered for reimbursement subject to a commercial PAS discount scheme. The discount value is not public knowledge and so is not included in base case analyses	Secukinumab is offered for reimbursement subject to a commercial PAS discount scheme. The discount value is not public knowledge and so is not included in base case analyses
Cost per dose (£) – PAS applied	[redacted]	NA	NA

BNF: British National Formulary; PAS: patient access scheme

Notes:

A: No dose escalation to 300 mg has been applied in the base case

B: Calculated based on the assumption that there are 365.25 days in a year.

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

Drug administration costs and resource use costs associated with upadacitinib and its comparators are presented in Table 24 and Table 25, respectively. All prices represent 2019/20 costs. During the ongoing NICE technology appraisal for upadacitinib for the treatment of AS (ID3848),[93] it was suggested by the evidence review group that the TB Heaf test that was commonly included for monitoring in previous appraisals for nr-axSpA (TA383,[29] TA718[2] and TA719[1]) is no longer used commonly in clinical practice and therefore, it is more appropriate to include the interferon gamma release assay. As such, this has been included in this analysis instead. Due to the comparable health outcomes of upadacitinib, ixekizumab and secukinumab (Section B.3.9), it has been assumed that resource utilisation for all three therapies would be identical. This assumption was supported by clinical feedback gained during expert interviews and previous NICE technology appraisals: TA383,[29] TA718[2] and TA719.[1] Monitoring costs have been included for completeness. However, different discontinuation rates have been examined in the scenario analysis.

Table 24. Summary of drug administration costs

Administration type	Cost per administration	Justification/ Source
First administration		
Subcutaneous injection	£48.00	Assumed one hour of nurse time for training at first administration. PSSRU 2020. Cost per working hour for nurse in Band 6.[53]
Oral	£0.00	Assumed no administration cost for oral treatment.
Subsequent administrations		
Subcutaneous injection	£0.00	Assumed self-administered following training.
Oral	£0.00	Assumed no administration costs for oral treatments.
PSSRU: Personal Social Services Research Unit		

Table 25. Resource costs of the intervention and comparator technologies

Resource component	Cost per component	Frequency of use (A)		Justification/Source
		Initial 3 months	Subsequent 3-month periods	
Specialist visits	£149.14	2	0.5	TA383[29]; Corbett et al. (2016)[94] NHS Reference costs 2019/20 (WF01A – Total HRG)[50]
Full blood count	£2.56	2	1	TA383[29]; Corbett et al. (2016)[94]; NHS Reference Costs 2019/20 (DAPS05 – Total Other Currencies)[50]
Erythrocyte sedimentation rate	£2.56	2	1	
Liver function test	£1.20	2	1	TA383[29]; Corbett et al. (2016)[94]; NHS Reference Costs 2019/20 (DAPS04 – Total Other Currencies)[50]
Urea and electrolytes test	£1.20	2	1	
Chest radiograph	£32.65	1	0.25	TA383[29]; Corbett et al. (2016)[94]; NHS Reference Costs 2019/20 (WF01B – CL – Diagnostic Imaging – First Attendance)[50]
Antinuclear antibodies	£7.35	1	0	TA383[29]; Corbett et al. (2016)[94]; NHS Reference Costs 2019/20 (DAPS06 – Total Other Currencies)[50]
DNA double-strand test	£7.35	1	0	
Interferon gamma release assay (B)	£116.84	1	0	Assumed replacement for TB Heaf test; Akubaker et al. (2018)[95]; inflated using PSSRU 2020[53]
MRI	£156.25	1	0	TA383[29]; Corbett et al. (2016)[94]; NHS Reference Costs 2019/20 (weighted average – RD01A,

				RD02A, RD03Z, RD04Z, RD05Z, RD06Z, RD07Z – Total HRG)[50]
CRP (B)	£7.22	1	0	TA383[29]; Corbett et al. (2016)[94]; Henriksson et al. (2010); inflated using PSSRU 2020[53]

DNA: deoxyribonucleic acid; NHS: National Health Service; PSSRU: Personal Social Services Research Unit

Notes

A: Resource use costs are applied to all patients receiving treatment equally across treatment arms

B: Cost could not be sourced from NHS Reference Costs and so the cost was sourced from contemporary literature and was inflated to 2020 costs using the 2020 PSSRU NHSCII pay and prices indices.

B.4.2.4 Adverse reaction unit costs and resource use

As described in Section B.3.10, treatment with upadacitinib was well tolerated with few serious adverse events, and a similar adverse event profile to that of the placebo during SELECT-AXIS 2, study 2. Furthermore, the similarity of the safety profile of upadacitinib to those of ixekizumab and secukinumab (Section B.3.10) supports the assumption that adverse event costs are expected to be similar between therapies. As the purpose of a cost-comparison analysis is to determine the difference between therapies in terms of their costs, no adverse event costs were included in this analysis, as they are not expected to impact the results and conclusions. This approach is supported by previous NICE technology appraisal TA497[41] and clinical feedback gathered during expert interviews.[4]

B.4.2.5 Miscellaneous unit costs and resource use

As described in Section B.3.9, upadacitinib is comparable to both ixekizumab and secukinumab in terms of health outcomes. Therefore, beyond the costs already outlined above (drug acquisition, administration and monitoring costs), no additional miscellaneous unit costs or resource use were identified or incorporated in the analysis.

B.4.2.6 Clinical expert validation

The monitoring frequencies and associated costs in the cost-comparison analysis were identified from previous NICE technology appraisals (TA383,[29] TA718[2] and TA719[1]). In each of these appraisals, this approach was deemed to be appropriate by NICE and the external review groups evaluating these appraisals, for use in the economic modelling of nr-axSpA. The opinion of clinical and health economic experts was sought during a series of interviews conducted prior to this submission (see Appendix M for further information on the interview process conducted) who agreed that the approach adopted is in line with current clinical practice.

B.4.2.7 Uncertainties in the inputs and assumptions

Some uncertainty exists as to the number of patients requiring training in order to self-administer subcutaneous injections. This is because some patients may have already received training in order to self-administer previous biologic treatments. Furthermore,

some companies provide self-injection training free of cost, although the proportion of patients receiving this training is unclear. In order to address this uncertainty, a scenario analysis has been conducted in which all administration costs for the comparators; both of which require self-injection of the therapy, has been set to zero. This analysis can be found in Section B.4.4.

Discontinuation is assumed to occur due to a loss of response or as a result of a severe adverse event. As the evidence presented shows that upadacitinib is similar to ixekizumab and secukinumab both in terms of its safety profile and efficacy, it therefore, follows that similar rates of discontinuation are to be expected, as presented in Table 22. Whilst a standard annual discontinuation rate of 6% has been applied in the base case, a higher rate of 11% as seen in AS models, has been applied in a scenario analysis in order to ascertain the influence a higher discontinuation rate would have upon the cost-comparison analysis. This scenario analysis can be found in Section B.4.4.

B.4.3 Base-case results

Results of the base case analysis are presented in Table 26. The cost-comparison analysis presented demonstrates that treatment with upadacitinib would be a cost-saving approach to nr-axSpA therapy in comparison to ixekizumab and secukinumab. The analysis shows that undiscounted estimated savings are expected to be [redacted] and [redacted] per patient in the first year versus ixekizumab and secukinumab, respectively. The expected undiscounted cost-savings of upadacitinib over the five-year period total [redacted] and [redacted] versus ixekizumab and secukinumab, respectively (all results are inclusive of a PAS applied to upadacitinib, no PAS was applied to either comparator).

Table 26. Base case cost-comparison results

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Proportion remaining on treatment at the end of the year						
Upadacitinib	94.00%	88.36%	83.06%	78.07%	73.39%	-
Ixekizumab	94.00%	88.36%	83.06%	78.07%	73.39%	-
Secukinumab	94.00%	88.36%	83.06%	78.07%	73.39%	-
Total number of doses per patient per year						
Upadacitinib	356.93	335.51	315.38	296.46	278.67	-
Ixekizumab	14.23	11.98	11.26	10.59	9.95	-
Secukinumab	15.73	11.02	10.36	9.74	9.16	-
Total undiscounted costs						
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	£16,959	£13,812	£12,983	£12,204	£11,472	£67,430
Secukinumab	£10,535	£7,049	£6,626	£6,228	£5,855	£36,293
Incremental undiscounted costs						
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notes: Acquisition costs for upadacitinib include a PAS discount. A negative incremental cost value represents a cost-saving for upadacitinib						

B.4.4 Sensitivity and scenario analyses

Three scenario analyses were undertaken: the first presents results over a greater time horizon (10-years; Table 27), the second addresses the uncertainty that exists concerning the discontinuation rate and the third addresses the uncertainty concerning administration costs.

The second scenario uses a higher discontinuation rate of 11% that is commonly used in economic evaluations of AS, such as those found in TA383, TA407 and TA718.[1,2,4,29] This discontinuation rate has been applied to all therapies in this analysis and provides further evidence of the robustness of the base case results that show upadacitinib offers a cost-saving approach to the treatment of nr-axSpA (Table 28).

The final scenario analysis has been conducted in order to measure the effect of removing the need to provide training for patients to self-inject either ixekizumab or secukinumab. The removal of the need for training could potentially be due to patients already being experienced in self-injecting a previous biologic therapy or due to free training provided by some companies. Therefore, in this scenario, all costs associated with training have been removed. As can be seen from the results presented in Table 29, the removal of administration costs for the comparators has a very limited effect that is only present in the first year of treatment and does not alter the overall result that upadacitinib offers cost-savings to the NHS versus both ixekizumab and secukinumab.

Table 27. Cost-comparison results – Scenario 1 – 10-year time horizon

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Total
Proportion remaining on treatment at the end of year											
Upadacitinib	94.00%	88.36%	83.06%	78.07%	73.39%	68.99%	64.85%	60.96%	57.30%	53.86%	-
Ixekizumab	94.00%	88.36%	83.06%	78.07%	73.39%	68.99%	64.85%	60.96%	57.30%	53.86%	-
Secukinumab	94.00%	88.36%	83.06%	78.07%	73.39%	68.99%	64.85%	60.96%	57.30%	53.86%	-
Total number of doses per patient per year											
Upadacitinib	356.93	335.51	315.38	296.46	278.67	261.95	246.23	231.46	217.57	204.52	
Ixekizumab	14.23	11.98	11.26	10.59	9.95	9.36	8.79	8.27	7.77	7.30	
Secukinumab	15.73	11.02	10.36	9.74	9.16	8.61	8.09	7.60	7.15	6.72	
Total undiscounted costs											
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	£16,959	£13,812	£12,983	£12,204	£11,472	£10,784	£10,137	£9,528	£8,957	£8,419	£115,255
Secukinumab	£10,535	£7,049	£6,626	£6,228	£5,855	£5,503	£5,173	£4,863	£4,571	£4,297	£60,700
Incremental undiscounted costs (A)											
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Acquisition costs for upadacitinib include a PAS discount

A: A negative value represents a cost-saving for upadacitinib

Table 28. Cost-comparison results – Scenario 2 – Applying an 11% annual discontinuation rate

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Proportion remaining on treatment at the end of year						
Upadacitinib	89.00%	79.21%	70.50%	62.74%	55.84%	-
Ixekizumab	89.00%	79.21%	70.50%	62.74%	55.84%	-
Secukinumab	89.00%	79.21%	70.50%	62.74%	55.84%	-
Total number of doses per patient per year						
Upadacitinib	349.82	311.34	277.09	246.61	219.48	-
Ixekizumab	13.98	11.12	9.90	8.81	7.84	-
Secukinumab	15.49	10.23	9.10	8.10	7.21	-
Total undiscounted costs						
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	£16,670	£12,817	£11,407	£10,152	£9,035	£60,082
Secukinumab	£10,386	£6,541	£5,821	£5,181	£4,611	£32,540
Incremental undiscounted costs (A)						
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Acquisition costs for upadacitinib include a PAS discount

A: A negative value represents a cost-saving for upadacitinib

Table 29. Cost-comparison results – Scenario 3 – Removal of administration costs

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Proportion remaining on treatment at the end of year						
Upadacitinib	94.00%	88.36%	83.06%	78.07%	73.39%	-
Ixekizumab	94.00%	88.36%	83.06%	78.07%	73.39%	-
Secukinumab	94.00%	88.36%	83.06%	78.07%	73.39%	-
Total number of doses per patient per year						
Upadacitinib	356.93	335.51	315.38	296.46	278.67	-
Ixekizumab	14.23	11.98	11.26	10.59	9.95	-
Secukinumab	15.73	11.02	10.36	9.74	9.16	-
Total undiscounted costs						
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	£16,911	£13,812	£12,983	£12,204	£11,472	£67,382
Secukinumab	£10,487	£7,049	£6,626	£6,228	£5,855	£36,245
Incremental undiscounted costs (A)						
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Acquisition costs for upadacitinib include a PAS discount

A: A negative value represents a cost-saving for upadacitinib

B.4.5 Subgroup analysis

No relevant subgroups were identified for analysis.

B.4.6 Interpretation and conclusions of economic evidence

The clinical evidence presented demonstrated the use of upadacitinib to be comparable to both ixekizumab and secukinumab as a therapy for nr-axSpA in the population under consideration. Upadacitinib has become well established, both in terms of its efficacy and safety profile in other disease areas where it has been licensed for a number of years, including RA and PsA. Evidence presented in this submission supports the use of upadacitinib for the treatment of nr-axSpA.

The cost-comparison analysis has shown potential cost-savings of up to [redacted] per year with the use of upadacitinib when the upadacitinib PAS discount is applied. Further to the advantages in terms of fulfilling an unmet need for both an oral therapy and a different mechanism of action in this disease area, the cost savings available due to the lower acquisition cost could provide significant advantages to the NHS.

Overall, when considering the patient population addressed in this submission: patients with active nr-axSpA with OSI who have responded inadequately to NSAIDs and who are not suitable for treatment with or whose condition is not controlled well enough by tumour necrosis factor TNFα inhibitors, upadacitinib has comparable health benefits and is cost-saving compared to the current comparators in the NICE recommended treatment pathway, ixekizumab and secukinumab.

B.5 References

1. National Institute for Health and Care Excellence. Secukinumab for treating non-radiographic axial spondyloarthritis Technology appraisal guidance [TA719]. 2021.
2. National Institute for Health and Care Excellence. Ixekizumab for treating axial spondyloarthritis Technology appraisal guidance [TA718]. 2021.
3. National Institute for Health and Care Excellence. Guide to the processes of technology appraisal Process and methods [PMG19]. 2018.
4. AbbVie / HEOR Ltd. Expert interview report: Upadacitinib for the treatment of nr-axSpA [data on file]. 2022.
5. European Medicines Agency. Cosentyx: EPAR - Product Information, Annex I - Summary of product characteristics. 2021.
6. European Medicines Agency. RINVOQ Annex 1 Summary of Product Characteristics. 2021.
7. National Institute for Health and Care Excellence. Upadacitinib for treating active non-radiographic axial spondyloarthritis [ID3958] Awaiting development [GID-TA10908]. 2021.
8. National Axial Spondyloarthritis Society. Facts & Figures. 2022.
9. Baraliakos X, Braun J. Non-radiographic axial spondyloarthritis and ankylosing spondylitis: what are the similarities and differences? RMD Open. 2015;1(Suppl 1):e000053.
10. Quinn S, Maguire S, O'shea FB, et al. POS0964 CHARACTERISTICS AND BURDEN OF DISEASE IN PATIENTS WITH RADIOGRAPHIC VERSUS NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS IN THE ANKYLOSING SPONDYLITIS REGISTRY OF IRELAND COHORT. Annals of the Rheumatic Diseases. 2021;80(Suppl 1):747-.
11. Protopopov M, Poddubnyy D. Radiographic progression in non-radiographic axial spondyloarthritis. Expert Rev Clin Immunol. 2018;14(6):525-33.
12. Keat A, Bennett AN, Gaffney K, et al. Should axial spondyloarthritis without radiographic changes be treated with anti-TNF agents? Rheumatol Int. 2017;37(3):327-36.
13. Webb D SL, Barnett R, Sengupta R, Marshall L, Hamilton J, Zhao S & Gaffney K. . Act on axial SpA: A Gold Standard time for the diagnosis of axial SpA. London: National Axial Spondyloarthritis Society. 2021.
14. Chimenti M-S, Alten R, D'Agostino M-A, et al. Sex-associated and gender-associated differences in the diagnosis and management of axial spondyloarthritis: addressing the unmet needs of female patients. RMD Open. 2021;7(3):e001681.
15. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet. 2017;390(10089):73-84.
16. Hamilton L, Gilbert A, Skerrett J, et al. Services for people with ankylosing spondylitis in the UK—a survey of rheumatologists and patients. Rheumatology. 2011;50(11):1991-8.
17. Worcester S. Prevalence, diagnosis of ankylosis spondylitis still elusive. Rheumatology News 74 2011.
18. National Axial Spondyloarthritis Society. Waiting 8.5 years for a diagnosis risks pushing people in the UK into poverty. 2022.
19. Novartis. Novartis Cosentyx® (secukinumab) recommended by NICE for adults with non-radiographic axial spondyloarthritis (nr-axSpA). 2021. Available from: Novartis Cosentyx® (secukinumab) recommended by NICE for adults with non-radiographic axial spondyloarthritis (nr-axSpA) [accessed 10/03/2022].
20. Yu Q, Genco, M, & Khan, MPH,. Axial Spondyloarthritis: Disease Landscape & Forecast. Decision Resources Group. 2019.
21. Michelena X, López-Medina C, Marzo-Ortega H. Non-radiographic versus radiographic axSpA: what's in a name? Rheumatology (Oxford, England). 2020;59(Suppl4):iv18-iv24.
22. Hunter T, Sandoval D, Booth N, et al. Comparing symptoms, treatment patterns, and quality of life of ankylosing spondylitis and non-radiographic axial spondyloarthritis patients in the USA: findings from a patient and rheumatologist Survey. Clinical rheumatology. 2021;40(8):3161-7.
23. Mogard E, Olofsson T, Bergman S, et al. Chronic Pain and Assessment of Pain Sensitivity in Patients With Axial Spondyloarthritis: Results From the SPARTAKUS Cohort. J Rheumatol. 2021;48(11):1672-9.
24. Barnett R, Ingram T, Sengupta R. Axial spondyloarthritis 10 years on: still looking for the lost tribe. Rheumatology (Oxford, England). 2020;59(Suppl4):iv25-iv37.
25. Strand V, Singh JA. Patient Burden of Axial Spondyloarthritis. J Clin Rheumatol. 2017;23(7):383-91.

26. Packham J. Optimizing outcomes for ankylosing spondylitis and axial spondyloarthritis patients: a holistic approach to care. Rheumatology (Oxford). 2018;57(suppl_6):vi29-vi34.
27. Burgos-Varga R, Wei JC-C, Rahman MU, et al. The prevalence and clinical characteristics of nonradiographic axial spondyloarthritis among patients with inflammatory back pain in rheumatology practices: a multinational, multicenter study. Arthritis research & therapy. 2016;18(1):132-.
28. National Institute for Health and Care Excellence. Spondyloarthritis in over 16s: diagnosis and management NICE guideline [NG65]. 2017.
29. National Institute for Health and Care Excellence. TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis Technology appraisal guidance [TA383]. 2016.
30. Zavodovsky BV, Sivordova LE. Cardiovascular safety of non-steroidal anti-inflammatory drugs in chronic inflammatory rheumatic diseases. Ter Arkh. 2018;90(8):101-6.
31. Liew JW, Ward MM, Reveille JD, et al. Nonsteroidal Antiinflammatory Drug Use and Association With Incident Hypertension in Ankylosing Spondylitis. Arthritis Care Res (Hoboken). 2020;72(11):1645-52.
32. Zochling J, Bohl-Bühler MH, Baraliakos X, et al. Nonsteroidal anti-inflammatory drug use in ankylosing spondylitis--a population-based survey. Clin Rheumatol. 2006;25(6):794-800.
33. Lazzaroni M, Bianchi Porro G. Gastrointestinal side-effects of traditional non-steroidal anti-inflammatory drugs and new formulations. Aliment Pharmacol Ther. 2004;20 Suppl 2:48-58.
34. Fragoulis GE, Siebert S. Treatment strategies in axial spondyloarthritis: what, when and how? Rheumatology (Oxford, England). 2020;59(Suppl4):iv79-iv89.
35. Deodhar A, Sandoval D, Holdsworth E, et al. Use and Switching of Biologic Therapy in Patients with Non-Radiographic Axial Spondyloarthritis: A Patient and Provider Survey in the United States. Rheumatology and therapy. 2020;7(2):415-23.
36. Michelena X, Zhao SS, Dubash S, et al. Similar biologic drug response regardless of radiographic status in axial spondyloarthritis: data from the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis registry. Rheumatology (Oxford, England). 2021;60(12):5795-800.
37. Ciurea A, Exer P, Weber U, et al. Does the reason for discontinuation of a first TNF inhibitor influence the effectiveness of a second TNF inhibitor in axial spondyloarthritis? Results from the Swiss Clinical Quality Management Cohort. Arthritis Res Ther. 2016;18:71.
38. European Medicines Agency. Taltz - EPAR product information, Annex I - Summary of product characteristics. 2022.
39. Joo W, Almario CV, Ishimori M, et al. Examining Treatment Decision-Making Among Patients With Axial Spondyloarthritis: Insights From a Conjoint Analysis Survey. ACR Open Rheumatol. 2020;2(7):391-400.
40. National Institute for Health and Care Excellence. Golimumab for treating non-radiographic axial spondyloarthritis Technology appraisal guidance [TA497]. 2018.
41. National Institute for Health and Care Excellence. Golimumab for treating non-radiographic axial spondyloarthritis [TA497]. 2018.
42. National Institute for Health and Care Excellence. Bimekizumab for treating moderate to severe plaque psoriasis [TA723]. 2021.
43. National Institute for Health and Care Excellence. Guselkumab for treating moderate to severe plaque psoriasis [TA521]. 2018.
44. British National Formulary. BNF. 2021.
45. European Medicines Agency. Cosentyx: EPAR - Product Information.
. 2020. Available at: [Accessed 29/10/20].
46. European Medicines Agency. Taltz - EPAR product information. 2021.
47. Baeten D, Sieper J, Braun J, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. N Engl J Med. 2015;373(26):2534-48.
48. van der Heijde D, Song IH, Pangan AL, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet. 2019;394(10214):2108-17.
49. National Institute for Health and Care Excellence. Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors. Technology appraisal guidance [TA407]. 2016.
50. NHS England. NHS reference costs 2019 to 2020. 2020.

51. Emery P, Van Keep M, Beard S, et al. Cost Effectiveness of Secukinumab for the Treatment of Active Ankylosing Spondylitis in the UK. Pharmacoeconomics. 2018;36(8):1015-27.
52. Corbett M, Soares M, Jhuti G, et al. Tumour necrosis factor-α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 2016;20(9):1-334, v-vi.
53. Curtis L BA. Unit Costs of Health and Social Care 2019. Kent, UK: Personal Social Services Research Unit;. 2019.
54. AbbVie. Protocol for Clinical Study M19-944 Axial Spondyloarthritis: Evaluation of Upadacitinib in Adult Subjects – SELECT-AXIS 2. Data on file. 2021.
55. AbbVie. Clinical study report: M19-944. A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of Upadacitinib in Adult Subjects with Axial Spondyloarthritis Followed by a Remission-Withdrawal Period. Data on file. 2021.
56. Hamilton L, Barkham N, Bhalla A, et al. BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. Rheumatology. 2016;56(2):313-6.
57. Deodhar A, Blanco R, Dokoupilová E, et al. Improvement of Signs and Symptoms of Nonradiographic Axial Spondyloarthritis in Patients Treated With Secukinumab: Primary Results of a Randomized, Placebo-Controlled Phase III Study. Arthritis Rheumatol. 2021;73(1):110-20.
58. Deodhar A, van der Heijde D, Gensler LS, et al. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. Lancet. 2020;395(10217):53-64.
59. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination 2009.
60. Hamilton L, Gilbert A, Skerrett J, et al. Services for people with ankylosing spondylitis in the UK--a survey of rheumatologists and patients. Rheumatology (Oxford). 2011;50(11):1991-8.
61. Hamilton L, Barkham N, Bhalla A, et al. BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. Rheumatology. 2017;56(2):313-6.
62. Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis. 2013;72(6):815-22.
63. Deodhar A, Gensler LS, Kay J, et al. A Fifty-Two-Week, Randomized, Placebo-Controlled Trial of Certolizumab Pegol in Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol. 2019;71(7):1101-11.
64. ClinicalTrials.gov. Multicenter Study Evaluating Certolizumab Pegol Compared to Placebo in Subjects With axSpA Without X-ray Evidence of AS (C-AXSPAND). 2021.
65. Deodhar A, Mease P, Rahman P, et al. Ixekizumab Improves Patient-Reported Outcomes in Non-Radiographic Axial Spondyloarthritis: Results from the Coast-X Trial. Rheumatology and therapy. 2021;8(1):135-50.
66. Poddubnyy D JX PC, Russ H, Schymura Y, Liu-Leage S, Haschemi Nassab M, Dudler J,. Achievement of Low Disease Activity According to BASDAI with Ixekizumab in Patients with Axial Spondyloarthritis: 16-Week Results from the COAST Trials [abstract]. Arthritis & Rheumatology. 2020;72(suppl 10).
67. Dougados M, van der Heijde D, Sieper J, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2014;66(8):2091-102.
68. ClinicalTrials.gov. Study Comparing Etanercept (ETN) Against a Placebo for Etanercept on a Background Nonsteroidal Anti Inflammatory Drug (NSAIDs) in the Treatment of Early Spondyloarthritis (SpA) Patients Who do Not Have X-ray Structural Changes (EMBARK) 2015.
69. Sieper J, van der Heijde D, Dougados M, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol. 2015;67(10):2702-12.
70. van der Heijde D, Dougados M, Maksymowych WP, et al. Long-term tolerability and efficacy of golimumab in active non-radiographic axial spondyloarthritis: results from open-label extension. Rheumatology (Oxford). 2022;61(2):617-27.

71. Haibel H, Rudwaleit M, Listing J, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Arthritis Rheum. 2008;58(7):1981-91.
72. Marzo-Ortega H DA BR, Kameda H, Kivitz A, Poddubnyy D, Magrey M, Wang J, Haemmerle S, Shete A, Braun J. ecukinumab Improves Pain, Morning Stiffness, Fatigue and Physical Function in Tumor Necrosis Factor Inhibitor-Naïve Patients with Non-Radiographic Axial Spondyloarthritis: Results from a Randomized Controlled Phase III Study [abstract]. Arthritis & Rheumatology. 2020;72(suppl 10).
73. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis. 2014;73(1):39-47.
74. Dias S WN, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials: National Institute for Health and Clinical Excellence;. 2011.
75. Gelman A, Rubin DB. Markov chain Monte Carlo methods in biostatistics. Statistical Methods in Medical Research. 1996;5(4):339-55.
76. Brooks SP, Gelman A. General Methods for Monitoring Convergence of Iterative Simulations. Journal of Computational and Graphical Statistics. 1998;7(4):434-55.
77. Dias SA AAEW, N.J.; Jansen, J.P.; Sutton, A.J. . Network Meta-Analysis for Decision-Making. First ed. Hoboken, NJ: John Wiley & Sons; . 2018.
78. Lambert PC, Sutton AJ, Burton PR, et al. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. Stat Med. 2005;24(15):2401-28.
79. Deodhar A, Yu D. Switching tumor necrosis factor inhibitors in the treatment of axial spondyloarthritis. Semin Arthritis Rheum. 2017;47(3):343-50.
80. Maksymowych WP, Kumke T, Auteri SE, et al. Predictors of long-term clinical response in patients with non-radiographic axial spondyloarthritis receiving certolizumab pegol. Arthritis Res Ther. 2021;23(1):274.
81. Sieper J, Landewé R, Magrey M, et al. Predictors of remission in patients with non-radiographic axial spondyloarthritis receiving open-label adalimumab in the ABILITY-3 study. RMD Open. 2019;5(1):e000917.
82. Neuenschwander R, Hebeisen M, Micheroli R, et al. Differences between men and women with nonradiographic axial spondyloarthritis: clinical characteristics and treatment effectiveness in a real-life prospective cohort. Arthritis Res Ther. 2020;22(1):233.
83. Sieper J, Rudwaleit M, Lenaerts J, et al. Partial remission in ankylosing spondylitis and non-radiographic axial spondyloarthritis in treatment with infliximab plus naproxen or naproxen alone: associations between partial remission and baseline disease characteristics. Rheumatology (Oxford). 2016;55(11):1946-53.
84. Achana FA, Cooper NJ, Dias S, et al. Extending methods for investigating the relationship between treatment effect and baseline risk from pairwise meta-analysis to network meta-analysis. Stat Med. 2013;32(5):752-71.
85. Deodhar A, Chakravarty SD, Cameron C, et al. A systematic review and network meta-analysis of current and investigational treatments for active ankylosing spondylitis. Clin Rheumatol. 2020;39(8):2307-15.
86. Cameron C, Hutton B, Druchok C, et al. Importance of assessing and adjusting for cross-study heterogeneity in network meta-analysis: a case study of psoriasis. J Comp Eff Res. 2018;7(11):1037-51.
87. Signorovitch JE, Betts KA, Yan YS, et al. Comparative efficacy of biological treatments for moderate-to-severe psoriasis: a network meta-analysis adjusting for cross-trial differences in reference arm response. Br J Dermatol. 2015;172(2):504-12.
88. Cameron C, Varu A, Lau A, et al. Incorporating adjustments for variability in control group response rates in network meta-analysis: a case study of biologics for rheumatoid arthritis. BMC Med Res Methodol. 2019;19(1):193.
89. San Koo B, Kim T-H. The role of ixekizumab in non-radiographic axial spondyloarthritis. Therapeutic advances in musculoskeletal disease. 2021;13:1759720X20986734-1759720X.
90. National Institute for Health and Care Excellence. Upadacitinib for treating active ankylosing spondylitis [ID3848] Document B Company evidence submission. 2021. Available at: [Accessed 07/03/2022].

91. National Institute for Health and Care Excellence. Upadacitinib for treating active ankylosing spondylitis ID3848 clarification questions. 2021. Available at: [Accessed
92. British National Formulary. Upadacitinib. 2021.
93. National Institute for Health and Care Excellence. Upadacitinib for treating active ankylosing spondylitis [ID3848]. 2022.
94. Corbett M, Soares M, Jhuti G, et al. Tumour necrosis factor-α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 2016;20(9):1-334, v-vi.
95. Abubakar I, Lalvani A, Southern J, et al. Two interferon gamma release assays for predicting active tuberculosis: the UK PREDICT TB prognostic test study. Health technology assessment (Winchester, England). 2018;22(56):1-96.

B.6 Appendices

In line with the user guide for company evidence submission template, appendices start at C, because Document A is the submission summary and Document B is the main submission.

Appendix number	Appendix Title	Location
C	Upadacitinib: SmPC and EPAR	Provided as a separate document
D	Identification, selection and synthesis of clinical evidence: systematic literature review report	Provided as a separate document
E	Subgroup analysis	Provided in Appendix J
F	Adverse reactions	Provided in the main body of the report (Section B.3.10) and Appendix J
G	Cost and healthcare resource identification, measurement and validation	Provided as a separate document
H	Price details of treatments included in the submission	Provided in the main body of the report (Section B.4.2, Table 23)
I	Checklist of confidential information	Provided as a separate document
J	SELECT-AXIS2: additional clinical data	Provided as a separate document
K	Clinical effectiveness NMA report	Provided as a separate document
M	Clinical expert validation	Provided as a separate document

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Upadacitinib for treating active non-radiographic axial spondyloarthritis ID3958

Clarification questions

June 2022

File name	Version	Contains confidential information	Date
		Yes	

Section A: Clarification on effectiveness data

Comparable clinical effectiveness of intervention and comparators

A1. Priority question. Network meta-analysis (NMA) results comparing upadacitinib versus ixekizumab and upadacitinib versus secukinumab are presented in the company submission (CS), Tables 16-19. The odds ratios show that there are no statistically significant differences between the intervention and the comparators. This does not necessarily mean that the intervention and comparator are "equivalent" or "similar". Please provide any additional information that supports the claim that upadacitinib has similar or greater health benefits than ixekizumab and/or secukinumab.

Across a wide range of NMAs, no statistically significant differences were found for upadacitinib versus secukinumab or ixekizumab for the treatment of nr-axSpA. On the basis of this evidence, it can be concluded that the efficacy of upadacitinib is not statistically different from these comparators. Further, this evidence indicates that the efficacy of upadacitinib is similar or comparable to those for secukinumab or ixekizumab.

This is the same basis on which previous NICE appraisals have concluded similarity between TNFα inhibitors for AS and nr-axSpA (TA383).[1] A similar NMA using the Bayesian methodology was used to demonstrate similarity between the TNFα inhibitors approved to treat nr-axSpA,[2] which, in the absence of direct head-to-head trials, was accepted to demonstrate similarity between the comparators by the Evidence Review Group.

It should be acknowledged that any uncertainty around comparability of evidence is in favour of improved outcomes for upadacitinib. Odds ratios and differences of the key NMA results are presented in Table 1 and are also shown in section B.3.9.2 of the CS. Although there are no statistical differences between upadacitinib and ixekizumab or secukinumab, numerical differences favour upadacitinib. Furthermore, clinical expert agreed that upadacitinib has comparable health benefits to ixekizumab and secukinumab.

Table 1. Summary of NMA results for upadacitinib versus key comparators

Endpoint		Comparison versus upadacitinib		
		PBO	IXE80Q4W	SEC150 (no LD)
ASAS40 Median odds ratio (95% CrI)	Overall population	[redacted]	[redacted]	[redacted]
	OSI population	[redacted]	[redacted]	[redacted]
BASDAI50 Median odds ratio (95% CrI)	Overall population	[redacted]	[redacted]	[redacted]
	OSI population	[redacted]	[redacted]	[redacted]
BASDAI CFB Median difference (95% CrI)	Overall population	[redacted]	[redacted]	[redacted]
	OSI population	[redacted]	[redacted]	[redacted]
BASFI CFB Median difference (95% CrI)	Overall population	[redacted]	[redacted]	[redacted]
	OSI population	[redacted]	[redacted]	[redacted]

**Indicates a statistically significant result.
Green cells indicate results that numerically favour upadacitinib; white cells indicate results that numerically favour the comparator.
Note: Overall population=OSI/mixed RCTs and Week 14 UPA; OSI population=OSI only RCTs and Week 14 UPA
Abbreviations: ASAS40: assessment of ankylosing spondylitis 40; BASDAI50: Bath ankylosing spondylitis disease activity score 50; BASDAI: Bath ankylosing spondylitis disease activity score; CFB: change from baseline; BASFI: Bath Ankylosing Spondylitis functional index; PBO: placebo; SEC: secukinumab; IXE: ixekizumab; LD: loading dose; FE=fixed effects unadjusted model; NA=not applicable (i.e., could not be included in network); CrI=credible interval; RCT=randomized clinical trial.

SELECT-AXIS 2 trial

A2. Reasons for prior biologic disease modifying anti-rheumatic drug (bDMARD) discontinuation at baseline (CS, Table 11) include "Lack of efficacy to TNFα inhibitors" and "Lack of efficacy to IL-17A inhibitors". To get a better understanding of prior bDMARD use in the SELECT-AXIS 2 trial, please complete the following table:

As requested, **Error! Not a valid bookmark self-reference.** presents prior bDMARD use in the population enrolled in the SELECT-AXIS 2, study 2 trial.[3] The SELECT-AXIS 2, study 2 trial included patients who were bDMARD-naïve (68.6% in the upadacitinib arm, 65.6% in the placebo arm) or bDMARD experienced (bDMARD-IR) (31.4% in the upadacitinib arm, 34.4% in the placebo arm) in line with the population defined in the NICE decision problem. Of the bDMARD-IR patients, most patients had

received prior TNFα inhibitors (28.2% in the upadacitinib arm, 27.4% in the placebo arm), with adalimumab being the most commonly received previous treatment (14.1% in the upadacitinib arm, 14.0% in the placebo arm). No patient had received 3 or more previous bDMARD treatments before enrolling in the trial.

Compared to the trials for the secukinumab and ixekizumab, SELECT-AXIS 2, study 2, recruited a higher proportion of bDMARD-IR patients. The percentages of the trial populations that were bDMARD-IR in the SELECT-AXIS 2 study 2 (upadacitinib), COAST-X (ixekizumab) and PREVENT (secukinumab) trials were 31.4%, 0% and 11.4% respectively. bDMARD-IR patients have a poorer prognosis than bDMARD-naïve patients, as the likelihood of successful treatment when switching to a different bDMARD after a previous inadequate response is decreased.[4] Therefore, the population of SELECT-AXIS 2, study 2 is considered a harder to treat population, so, the NMA results for upadacitinib could be considered conservative when compared to its comparators. Additionally, the higher proportion of bDMARD-IR patients in SELECT-AXIS 2, study 2 was thought to be more representative of UK NHS patients by clinical experts.[5]

Table 2. Prior bDMARD use in the SELECT-AXIS 2, study 2 trial

Prior bDMARD use	Placebo	Upadacitinib
Number of prior bDMARDs		
Patients with ≥2 prior bDMARDs, n (%)	[redacted]	[redacted]
Patients with ≥3 prior bDMARDs, n (%)	[redacted]	[redacted]
Type of prior bDMARDs		
Patients with ≥2 prior TNFα inhibitors, n (%)	[redacted]	[redacted]
Patients with ≥2 prior IL-17 inhibitors, n (%)	[redacted]	[redacted]
Patients who received ≥1 TNFα inhibitor and ≥1 IL-17 inhibitor, n (%)	[redacted]	[redacted]
Patients with at least 1 prior TNF inhibitor, n (%)	[redacted]	[redacted]
Patients with at least 1 prior IL-17 inhibitor, n (%)	[redacted]	[redacted]

A3. It is stated in the CS, Section B.3.4.1 (Table 9) that: "Rubin's method will be used to combine the results from the multiple datasets".

i. **Please provide further information on the use of multiple imputation and the sensitivity analyses performed; for example, please state which variables were used.**

Binary Endpoints

The primary analysis is Non-Responder Imputation in conjunction with Multiple Imputation (NRI-MI). In NRI-MI, the missing data due to COVID-19 infection or logistical restriction was handled by Multiple Imputation (MI) and the missing data due to other reasons was handled by non-responder imputation (NRI). In addition, subjects who prematurely discontinue study drug or use rescue therapy were categorised as non-responders for visits after study drug discontinuation or rescue initiation.

To generate the MI datasets for the binary endpoints, we first generated the MI data for the continuous variables that were used for the derivation of the binary endpoints (e.g. ACR components) and then derived the binary endpoints from it. The imputation model for the continuous variables included screening hsCRP, screening MRI status (+/-), gender, race (white vs. non-white), ethnicity, age, baseline BMI, geographic region, duration since nr-axSpA diagnosis, duration of nr-axSpA symptom, prior bDMARD use, baseline value as well as longitudinal values (observed at any other visits).

CMH test was performed for each ‘complete’ dataset adjusting for the main stratification factors to test the treatment difference of upadacitinib versus placebo. The results from the 30 'complete' datasets were synthesised using Rubin's method.

In addition, NRI was conducted as a sensitivity analysis for binary endpoints where the missing data due to COVID-19 was also categorised as non-responders. Results from sensitivity analysis were consistent with the primary NRI-MI analysis. Other supplementary analyses using as observed (AO), AO-NRI, AO-MI etc. and tipping point analyses were performed as well and showed consistent results as the primary analysis, which demonstrated the robustness of the primary analysis for the efficacy endpoints regardless of the handling of intercurrent events or assumption of missing data.

Continuous Endpoints

MI with or without tipping point analysis were performed as sensitivity analysis for the continuous endpoints while MMRM (mixed model repeated measures) was performed for the primary analysis. The imputation model for MI included screening hsCRP,

screening MRI status (+/-), gender, race (white vs. non-white), ethnicity, age, baseline BMI, geographic region, duration since nr-axSpA diagnosis, duration of nr-axSpA symptom, prior bDMARD use, baseline value as well as longitudinal values for the outcome variable.

ii. Do you consider that the missing at random assumption is reasonable where patients are likely to miss appointments because of pain?

Missing at random can be described as systemic differences in data which are related to the observed data and not unobserved data.[6]

For the binary endpoints, only missing due to COVID-19 was imputed by MI assuming MAR for the primary analysis (NRI-MI). Other missing or intercurrent events are categorised as non-responders. The reason is because the COVID-19 pandemic was interfering with the conduct of SELECT-AXIS 2, study 2, with potential impacts on treatment duration and the collection, analysis and the interpretation of clinical trial data. Some protocol-specified visits in the clinical trials were impacted due to COVID-19 infection or logistical restrictions during the pandemic. The probability of having missed visits and missing data due to COVID-19 can be reasonably assumed to be unrelated to the unobserved values, and reasonably assume that these missing data due to COVID-19 are missing at random (MAR). Sensitivity and supplementary analyses were performed for the robustness of the primary analysis and discussed above.

For the continuous endpoints, MMRM model was performed for the primary analysis. Additionally, to assess the impact of potential departures from the missing-at-random assumption, tipping point analyses were conducted as a sensitivity check for change from baseline in multiplicity-controlled secondary continuous endpoints at Week 14. Results from the tipping point analysis were consistent with the primary analysis and demonstrated that the primary analysis is robust to the missing not at random (MNAR) assumption. Under the most conservative assumption that all subjects with missing data in the upadacitinib group were non-responders and all subjects with missing data in the placebo group were responders, the P-value remained ≤ 0.01 for the comparison of upadacitinib vs placebo in favour of upadacitinib.[3]

NMAs presented by the company

A4. Priority question. The description of the models and populations used in the NMAs is unclear. Please clarify the following EAG understanding is correct:

- **The 'OSI population' referred to in the CS, Tables 16-19 aligns with NMA 3 in the NMA report (CS, Appendix K), i.e. "nr-AxSpA with OSI RCTs only, using Week 14 outcomes for UPA".**
- **The 'Full population' referred to in the CS, Tables 16-19 aligns with NMA 1 in the NMA report (CS, Appendix K), i.e. "All relevant RCTs included, prioritizing nr-AxSpA with OSI data, using Week 14 outcomes for UPA".**
- **No results are presented in the CS for NMA 5 in the NMA report (CS, Appendix K), i.e. "All relevant RCTs included, prioritizing overall population data, using Week 14 outcomes for UPA".**

The EAG's understanding of the models and the populations used in the NMAs is correct. NMAs 1 and 3 are considered the most relevant to this submission.

- NMA 3 (OSI population) considers nr-axSpA patients with OSI and week 14 outcomes for upadacitinib. NMA 3 is considered the primary NMA in the CS as it aligns with the patient population presented in the NICE decision problem.

- NMA 1 (Full population) includes all relevant RCTs of nr-axSpA patients with or without OSI, prioritising OSI patients where data is available, and uses week 14 outcomes for upadacitinib. NMA 1 is included for completeness as it was informed by more trial data. The results of NMA 1 align with those from NMA 3, demonstrating no significant differences between upadacitinib, secukinumab and ixekizumab.

- NMA 5 includes all relevant RCTs of nr-axSpA patients and uses week 14 outcomes for upadacitinib but prioritises the overall population over the OSI population. Therefore, it was not presented in the main submission as it was considered less relevant to the patient population defined in the NICE decision problem.

Week 14 was considered the most appropriate timeframe over week 12 as it is more representative of the treatment response assessment time points used in previous appraisals.[7,8] The NICE guideline (NG65) recommends assessing response to bDMARDs treatments after week 12 or week 16.[9] Previous HTAs have used varying timepoints for assessment: while TA383[1] used 12 weeks, TA407[10] and TA718[8] used 16 weeks for synthesis of clinical outcomes. The NMA presented in the company submission uses week 14 outcomes, which is aligned with clinician opinion. Further, NMA scenarios considered alternative approaches and conclusions are aligned with the main analyses. Multiple supportive NMAs were conducted due to data sparsity, which demonstrated similar results to the primary NMA (NMA 1), where upadacitinib has similar efficacy to secukinumab and ixekizumab.

Table 3 illustrates all NMAs conducted and outlines the populations and timepoints used.

Table 3. NMAs conducted

Description in NMA report (Appendix K)	**NMA 1**	NMA 2	**NMA 3**	NMA 4	NMA 5	NMA 6
Description in CS	**Full population (NMA 1)**	-	**OSI population (NMA 3)**	-	-	-
Population	**All relevant RCTs included, prioritising nr-axSpA patients with OSI data**	All relevant RCTs included, prioritising nr-axSpA patients with OSI data	**nr-AxSpA with OSI RCTs only**	nr-AxSpA with OSI RCTs only	All relevant RCTs included, prioritising overall population data	All relevant RCTs included, prioritising overall population data
Timepoint	**Week 14**	Week 12	**Week 14**	Week 12	Week 14	Week 12

A5. Priority question. There appear to be several discrepancies between the results reported in the CS, Tables 16-19 and the results reported in the NMA report (CS, Appendix K).

i. **Please clarify all the results presented in Tables 16-19 are correct and please provide updated tables if any are incorrect.**

The company submission included typographical errors. Please find updated Tables 16-19 below containing the correct NMA results.

Table 16. Odds ratios of ASAS40 for upadacitinib versus comparators – Week 14

	OSI population			Full Population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC150 no LD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks; SEC150 (no LD): secukinumab 150mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; OSI: objective signs of inflammation;

Table 17. Odds ratios of BASDAI50 for upadacitinib versus comparators – Week 14

	OSI population			Full population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150 no LD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks SEC150 (no LD): secukinumab 150/300 mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; OSI: objective signs of inflammation;

Table 18. Relative effect of BASDAI CFB for upadacitinib versus comparators – Week 14

	OSI population			Full population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150 no LD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks; SEC150(no LD): secukinumab 150 mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; OSI: objective signs of inflammation;

Table 19. Relative effect of BASFI CFB for upadacitinib versus comparators – Week 14

	OSI population			Full population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150 no LD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks; SEC150 (no LD): secukinumab 150 mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; OSI: objective signs of inflammation;

ii. Please supply a Microsoft Excel file or tables with the data used in each reported NMA (Tables 16-19).

As found in Appendix K, sub-appendix A of the CS, Table 4 and Table 5 show the data used to inform in each NMA reported. This data informs the tables presented in A5i, Tables 16-19, the CS, and Tables 40, 43, 46 and 49 in the clinical effectiveness NMA report (Appendix K of the CS).

Table 4. Data for binary outcomes – ASAS40 (Table 16 in the CS) and BASDAI 50 (Table 17 in the CS)

Study	Treatment arm	Outcome timepoint (week)	ASAS40: N assessed	ASAS40: N responded	BASDAI50: N assessed	BASDAI50: N responded
ABILITY-1	PBO	12	94	14	94	14
ABILITY-1	ADA40	12	91	33	91	32
ABILITY-1 (OSI)	PBO	12	73	10	73	10
ABILITY-1 (OSI)	ADA40	12	69	28	69	27
c-axSpAnd	PBO	12	158	18	NR	NR
c-axSpAnd	CZP200	12	159	76	NR	NR
COAST-X	PBO	16	105	20	105	15
COAST-X	IXE80Q2W	16	102	41	102	34
COAST-X	IXE80Q4W	16	96	34	96	30
EMBARK	PBO	12	108	17	109	26
EMBARK	ETN50	12	105	34	105	46
EMBARK (OSI)	PBO	12	95	16	NR	NR
EMBARK (OSI)	ETN50	12	94	33	NR	NR
GO-AHEAD	PBO	16	100	23	100	30
GO-AHEAD	GOL50	16	97	55	97	57
GO-AHEAD (OSI)	PBO	16	80	18	80	23
GO-AHEAD (OSI)	GOL50	16	78	47	78	46
Haibel et al. 2008	PBO	12	24	3	24	5
Haibel et al. 2008	ADA40	12	22	12	22	11
PREVENT	PBO	16	186	52	186	39
PREVENT	SEC150	16	185	74	185	69
PREVENT	SEC150 (no LD)	16	184	75	184	69
RAPID-axSpA	PBO	12	50	8	50	8
RAPID-axSpA	CZP200	12	46	22	46	23
RAPID-axSpA	CZP400	12	51	24	51	24
SELECT-AXIS-2 (wk 12)	PBO	12	157	36	157	30
SELECT-AXIS-2 (wk 12)	UPA15	12	156	72	156	64
SELECT-AXIS-2 (wk 14)	PBO	14	157	35	157	35
SELECT-AXIS-2 (wk 14)	UPA15	14	156	70	156	66

ASAS=Assessment of Spondyloarthritis International Society Criteria; ASAS40=≥40% improvement in ASAS; BASDAI50=≥50% improvement in BASDAI; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; N=sample size; NR=not reported.

Table 5. Data for continuous outcomes – BASDAI CFB (Table 18 in the CS) and BASFI CFB (Table 19 in the CS)

Study	Treatment arm	Outcome timepoint (week)	N randomized	BASDAI CFB: Endpoint N	BASDAI CFB: Mean (SE)	BASFI CFB: Endpoint N	BASFI CFB: Mean (SE)
ABILITY-1	PBO	12	94	94	-1.000 (0.520)	94	-0.600 (0.560)
ABILITY-1	ADA40	12	91	91	-1.900 (0.520)	91	-1.100 (0.560)
ABILITY-1 (OSI)	PBO	12	73	73	-1.100 (0.230)	73	-0.630 (0.210)
ABILITY-1 (OSI)	ADA40	12	69	69	-2.200 (0.300)	69	-1.280 (0.240)
c-axSpAnd	PBO	12	158	158	-0.910 (0.220)	158	-0.380 (0.210)
c-axSpAnd	CZP200	12	159	159	-2.730 (0.210)	159	-2.070 (0.200)
COAST-X	PBO	16	105	105	-1.510 (0.220)	105	-1.340 (0.230)
COAST-X	IXE80Q2W	16	102	102	-2.520 (0.220)	102	-2.280 (0.230)
COAST-X	IXE80Q4W	16	96	96	-2.180 (0.220)	96	-2.010 (0.230)
EMBARK	PBO	12	109	94	-1.300 (0.300)	94	-0.800 (0.200)
EMBARK	ETN50	12	106	91	-2.000 (0.300)	91	-1.400 (0.200)
EMBARK (OSI)	PBO	12	95	NR	NR	NR	NR
EMBARK (OSI)	ETN50	12	94	NR	NR	NR	NR
GO-AHEAD	PBO	16	100	96	-1.600 (0.255)	97	-0.800 (0.213)
GO-AHEAD	GOL50	16	98	93	-3.700 (0.259)	93	-2.800 (0.259)
GO-AHEAD (OSI)	PBO	16	80	80	-1.510 (0.280)	80	-0.870 (0.250)
GO-AHEAD (OSI)	GOL50	16	78	78	-3.690 (0.280)	78	-2.780 (0.250)
Haibel et al. 2008	PBO	12	24	24	-1.200 (0.480)†	24	-0.800 (0.560)†
Haibel et al. 2008	ADA40	12	22	22	-2.700 (0.520)†	22	-2.400 (0.530)†
PREVENT	PBO	16	186	186	-1.460 (0.210)	186	-1.010 (0.210)
PREVENT	SEC150	16	185	185	-2.350 (0.200)	185	-1.750 (0.200)
PREVENT	SEC150 (no LD)	16	184	184	-2.430 (0.200)	184	-1.640 (0.200)
RAPID-axSpA	PBO	12	50	50	-1.500 (0.400)	50	-0.400 (0.400)
RAPID-axSpA	CZP200	12	46	46	-3.300 (0.400)	46	-2.300 (0.400)
RAPID-axSpA	CZP400	12	51	51	-3.400 (0.400)	51	-2.300 (0.400)
SELECT-AXIS-2 (wk 12)	PBO	12	157	156	-1.550 (0.161)	156	-1.390 (0.156)
SELECT-AXIS-2 (wk 12)	UPA15	12	156	154	-2.870 (0.161)	154	-2.530 (0.158)
SELECT-AXIS-2 (wk 14)	PBO	14	157	156	-1.810 (0.163)	156	-1.470 (0.163)
SELECT-AXIS-2 (wk 14)	UPA15	14	156	154	-2.860 (0.166)	154	-2.610 (0.166)

BASFI=Bath Ankylosing Spondylitis Functional Index; CFB=change from baseline; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; N=sample size; NR=not reported; SE=standard error.

A6. Regarding data imputation and assumptions (CS, Appendix K, NMA report section 4.5.1), were there any cases where medians were used to estimate means, or inter-quartile ranges were used to estimate standard errors?

Following the imputation methods laid out in Section 4.5.1. of Appendix K, the NMA report, these data values were imputed for the NMA (when mean and/or standard error were not directly reported in a primary or secondary source):

- Haibel 2008 (BASDAI CFB, BASFI CFB for ADA40/PBO): mean change was imputed from baseline and week 12 values. Note that SE values were reported in TA719, and therefore not imputed.
- Haibel 2008 (ASAS40, ASAS20, ASASPR for ADA40/PBO): number of responders was imputed from overall N and reported percentage of responders.
- GO-AHEAD (full population, ASAS40, ASAS20 for GOL50/PBO): number of responders was imputed from overall N and reported percentage of responders.
- Rapid-AxSpA (ASAS40 for CZP200/CZP400/PBO): number of responders was imputed from overall N and reported percentage of responders.
- COAST-X (BASDAI50 for IXE80Q2W/IXE80Q4W/PBO): number of responders was imputed from overall N and reported percentage of responders.
- C-AxSpAnd (Total Back Pain CFB for CZP200/PBO): mean change was imputed from baseline and week 12 values. SD/SE imputed using formula specified in section 4.5.1.
- EMBARK (full population, ASASPR for ETN50/PBO): number of responders was imputed from overall N and reported percentage of responders
- ABILITY-1 (full population, ASAS20, ASASPR, BASDAI50 for ADA40/PBO): number of responders was imputed from overall N and reported percentage of responders

Additional NMAs requested by the EAG

A7. Priority question. Including trials of irrelevant comparators (TNFα inhibitors) and irrelevant populations (patients receiving treatment with TNFα inhibitors and some patients without objective signs of inflammation) introduces unnecessary heterogeneity into the NMAs. Please carry out NMAs which *only* include trials of upadacitinib, ixekizumab and secukinumab (i.e., the SELECT-AXIS 2, COAST-X and PREVENT trials, respectively) for the following outcomes: ASAS 40, BASDAI 50, BASDAI CFB and BASFI CFB (CS, Tables 16-19).

Table 6 to Table 9 summarise the results for the additional NMA including only upadacitinib, ixekizumab and secukinumab for the four key outcomes at week 12 and 14. NMAs could only be conducted for the OSI population as SELECT-AXIS 2, COAST-X and PREVENT trials included patients with OSI only.

Table 6. Odds ratios of ASAS40 for upadacitinib versus comparators – Week 14

	OSI Population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
SEC150 no LD	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]

* Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks; SEC150(no LD): secukinumab 150 mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio;

Table 7. Odds ratios of BASDAI50 for upadacitinib versus comparators – Week 14

	OSI Population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
SEC150 no LD	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]

* Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks; SEC150(no LD): secukinumab 150 mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio;

Table 8. Relative effect of BASDAI CFB for upadacitinib versus comparators – Week 14

	OSI Population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
SEC150 no LD	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]

* Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks; SEC150(no LD): secukinumab 150 mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio;

Table 9. Relative effect of BASFI CFB for upadacitinib versus comparators – Week 14

	Full Population		
FE model	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
UPA15	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
SEC150 no LD	[redacted]	[redacted]	[redacted]
IXE80Q4W	[redacted]	[redacted]	[redacted]

* Indicates a statistically significant result.
Treatments: IXE80Q4W: ixekizumab 80 mg every 4 weeks; SEC150(no LD): secukinumab 150 mg (no loading dose); UPA15: upadacitinib 15 mg,
CrI: credible interval; FE: fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio;

Section B: Clarification on cost effectiveness data

The EAG has no cost effectiveness clarification questions.

Section C: Textual clarification and additional points

The EAG has no additional clarification questions.

References

1. National Institute for Health and Care Excellence. TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis Technology appraisal guidance [TA383]. 2016. Available at: https://www.nice.org.uk/guidance/ta383 [Accessed 08/03/2022].
2. Corbett M, Soares M, Jhuti G, et al. Tumour necrosis factor-α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. Health Technol Assess. 2016;20(9):1-334, v-vi.
3. AbbVie. Clinical study report: M19-944. A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of Upadacitinib in Adult Subjects with Axial Spondyloarthritis Followed by a Remission-Withdrawal Period. Data on file. 2021.
4. Ciurea A, Exer P, Weber U, et al. Does the reason for discontinuation of a first TNF inhibitor influence the effectiveness of a second TNF inhibitor in axial spondyloarthritis? Results from the Swiss Clinical Quality Management Cohort. Arthritis Res Ther. 2016;18:71.
5. AbbVie / HEOR Ltd. Expert interview report: Upadacitinib for the treatment of nr-axSpA [data on file]. 2022.
6. Mack C, Su Z, Westreich D. AHRQ Methods for Effective Health Care. Managing Missing Data in Patient Registries: Addendum to Registries for Evaluating Patient Outcomes: A User's Guide, Third Edition. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018.
7. National Institute for Health and Care Excellence. Secukinumab for treating non-radiographic axial spondyloarthritis Technology appraisal guidance [TA719]. 2021. Available at: https://www.nice.org.uk/guidance/ta719/chapter/1-Recommendations [Accessed 08/03/2022].
8. National Institute for Health and Care Excellence. Ixekizumab for treating axial spondyloarthritis Technology appraisal guidance [TA718]. 2021. Available at: https://www.nice.org.uk/guidance/ta718/chapter/1-Recommendations [Accessed 08/03/2022].
9. National Institute for Health and Care Excellence. Spondyloarthritis in over 16s: diagnosis and management. 2017. Available at: [Accessed 08/03/2021].
10. National Institute for Health and Care Excellence. Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors. Technology appraisal guidance [TA407]. 2016. Available at: [Accessed 08/03/2021].

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for treating active non-radiographic axial spondyloarthritis ID3958

Professional organisation submission

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	Spondyloarthritis Special Interest Group
2. Name of organisation	British Society for Rheumatology
3. Job title or position	Chair, Spondyloarthritis Special Interest Group
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	British Society for Rheumatology
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	We received funding from Abbvie, Amgen, Lilly, Pfizer, UCB and Novartis as exhibitors at our 2022 Annual Conference. We also received funding for our registers from Amgen, Sandoz and Lilly.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• Reduce disease activity • Improve pain and functioning • Improve quality of life (QoL) • Reduce fatigue • Reduce structural progression and radiographic change
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in BASDAI and spinal pain VAS by 2 points
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – in those patients who fail to respond to TNF inhibitors and / or IL-17 inhibitors. There is also a need for oral small molecule inhibitors for non-radiographic axial spondyloarthritis

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	In general or specialist outpatient clinics
9a. Are any clinical guidelines used in the	NICE guidance on management of spondyloarthritis

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway of care is generally well-defined but there may be local variability depending on local expertise, resources and agreement regarding funding of targeted therapies
9c. What impact would the technology have on the current pathway of care?	Provide additional options for medical management in those patients who have not responded to standard therapies
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes as an additional therapeutic option, managed in the same setting as current care
10a. How does healthcare resource use differ between the technology and current care?	This is the first oral small molecule agent in the treatment of non-radiographic axial spondyloarthritis
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – especially for patients who have not responded to currently approved medical therapies
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, for patients who have not responded to currently approved medical therapies
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	The technology may be easier for some patients, being orally administered rather than subcutaneous.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Disease activity measures to decide if the patient is eligible to start and continue treatment, used in the same way as for existing therapies. No additional testing.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – improve pain, disease activity, and quality of life for patients who have not responded to used therapies currently in use
16a. Is the technology a 'step-change' in the management of the condition?	Yes – a drug with a new mechanism of action

16b. Does the use of the technology address any particular unmet need of the patient population?	There is a significant unmet need for a group of patients who fail to respond, or lose response, to TNF or IL-17 inhibitors and this technology will offer an alternative treatment option
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As with all the medical therapies used in nr-axial spondyloarthritis, the risk of side effects will be weighed against the impact of uncontrolled disease. For some patients, active disease impairs their quality of life significantly and justifies the use of new medication with potential side effects.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes ASAS responses, also CRP, quality of life measures, fatigue, and metrology.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were	No new safety risks identified that we are aware of

not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	
21. How do data on real-world experience compare with the trial data?	Not aware of real-world data

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Significant unmet need exists for patients with nr-AxSpA, due to failure of response or loss of response to existing therapies and this technology offers an additional therapeutic option • First of its kind oral small molecule targeted therapy for nr-AxSpA • Provides convenience for patients as simple administration compared to injections • • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for treating active non-radiographic axial spondyloarthritis [ID3958]

Patient Organisation Submission

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

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

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	Jill Hamilton		
2. Name of organisation	National Axial Spondyloarthritis Society		
3. Job title or position	Head of Policy and Health Services		
4a. Brief description of the organisation (including who funds it). How many members does it have?	NASS is the only charity in the UK solely dedicated to supporting people living with axial spondyloarthritis (axial SpA) including ankylosing spondylitis. We provide information and support to people with the condition, as well as campaigning for better treatment and care. NASS is funded by a variety of voluntary sources including membership, individual fundraisers, charitable trusts, legacies and industry funding. We receive no statutory or government funding. NASS currently has 4,071 members, the majority of which have axial SpA (AS).		
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months?	Abbvie Ltd	Aspiring to Excellence project	30,000
	UCB Pharma	NASS All Party Parliamentary Group.	16,000
	GlaxoSmithKline Ser U/Ltd	Patient recruitment to clinical trial	810
	UCB Pharma	NASS Gold Standard 2021 project funding	287,681
	Biogen Idec Ltd	Aspiring to Excellence Program	30,000
	Novartis Pharmaceuticals UK Ltd	Funding for APPG	16,000
	Novartis Pharmaceuticals UK Ltd	Funding for round table meeting	11,900
	Novartis Pharmaceuticals UK Ltd	Aspiring to Excellence programme	30,000
	Eli Lilly and Company	Aspiring to Excellence programme for 2022	30,000
	Janssen-Cilag Ltd	Core funding	5,000

[Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	A survey was conducted for ID3848 seeking views on the availability of upadacitinib for ankylosoing spondylitis. As the questions asked would be largely the same it is safe to assume that the response to the possibility of this drug becoming available for those on a different stage of the spectrum of disease would be the same. We received 192 eligible responses to this survey. Respondents were people with non-radiographic axial spondyloarthritis, people with ankylosing spondylitis and carers.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Axial Spondyloarthritis (axial SpA) refers to inflammatory disease where the main symptom is back pain, and where the x-ray changes of sacroiliitis *may or may not* be present. Within axial SpA there are two groups: **Ankylosing Spondylitis (AS):** Where the x-ray changes are clearly present. **Non-radiographic axial spondyloarthritis (nr-axSpA):** Where x-ray changes are *not* present but you have symptoms. Axial SpA is an inflammatory condition of the spine which often produces pain, stiffness, deformity and disability throughout adult life. It is a chronic progressive disease. It is characterised by periods of fluctuating intensity, leading to slowly increasing spinal and peripheral joint damage. People with ankylosing spondylitis often develop spinal fusion which is irreversible. We asked people to tell us about how having axial spondyloarthritis had impacted on their life. 92% said that it had impacted very (49%) or somewhat negatively (43%) . Most commonly people cited the pain and fatigue which impacted on their ability to carry on with everyday life. Many have had to stop working. The resulting effect on mental health was also a strong factor. *“I am in pain, every day. I suffer with severe fatigue and “brain fog” regularly. I can no longer work full time and am considering medical retirement at 45.”* *“My whole lifestyle has been impacted by AS it has turned me from a healthy, active & happy person into the complete opposite I’m now disabled, inactive & suffer with poor mental health.”* *“I was completely disabled by the pain. I lost my home and my career as a sports journalist and have never got that back. I spent 15 years barely able to function, on and off. I’d be dead without Humira; I was rationally considering suicide before being prescribed anti-TNF in 2004. I was on Etanercept but it didn’t really work. I finally switched to Humira in 2015 and am generally much better, but still have a lot of nerve pain.”*

	"My income has been less and therefore my pension is now less. It had affected my family relationships too." *"Divorce, premature retirement due to ill health, financial implications, no children, difficulty with relationships/ social life, difficulty exercising and travelling. lack of energy to do daily tasks of living."* *"It's affected me massively as I used to be a professional dancer and I compare myself to then and now and it can be quite mentally tough to deal with - it becomes a before life and a now with AS life."*

7. What do patients or carers think of current treatments and care available on the NHS?	We asked respondents to tell us which medications they were taking and to let us know their satisfaction levels. The majority were taking biologics (67%) and / or anti inflammatories (52%), with 14% needing opioids such as tramadol or morphine. Simple pain relief such as paracetamol (16%) and co-codamol (22%) were also being used. Respondents were relatively satisfied with their current medications, although just 15% were completely satisfied overall and 14% were completely satisfied with how it works for them. 26% of people were either were completely unsatisfied (6%) or somewhat unsatisfied (20%) with their medications overall. The weighted averages, when scored out of five were: • Overall satisfaction 3.44 • How well it works 3.49 • Side effects 3.54 • Convenience 3.71 Given the huge negative impact axial SpA is having on lives, there is clear room for improvement in medications.
8. Is there an unmet need for patients with this condition?	Yes. Yes. Whilst the corner stones of treatment are anti inflammatory medication and exercise, there are those who cannot tolerate non-steroidal anti inflammatories (NSAIDs) and 20% of people do not respond to biologic drugs currently available. A new drug targeting a different enzyme could mean an alternative treatment to enable people with non radiographic axial spondyloarthritis to be able to exercise more easily and to live a fuller life. At the present time this would be the only JAK inhibitor available to people with axial spondyloarthritis.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	When asked what advantages the technology may have over current medications: • 84% liked that is in tablet form • 54% thought it would be easy to store • 43% liked that it had already been used in other conditions • 30% thought the advantage came from the new formulation • 29% thought it sounded like it works well. Link to the information on the NICE website was included but no specific information on efficacy was included. In the open ended responses, respondents thought it may be cheaper than other biologics which are injected and that it would help those who have needle phobia. It was also mentioned that it would be easier to carry when travelling.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We also asked what concerns people might have and what they thought the disadvantages might be: • 75% of people were concerned about the side effects • 58% of people worried it wouldn't be as effective as current medications • 21% thought there may be issues with it being a new formula In the open ended responses, there were concerns about eligibility, the dosage, if a return to other treatment would be permitted if this was not effective, the possible interactions with other medications and if it caused infections.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There are a number of people who might benefit more such as those who: • Cannot tolerate NSAIDs • Have not responded to other biologics • Have a needle phobia • Live in shared accommodation and do not have access to their own fridge to store other biologic drugs • Travel lots for work or want to go travelling.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes. Those from lower income households who may need to share access to communal areas. This would also apply to students and young people who often have shared accommodation.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The drug was well received by patient and their carers. • The current satisfaction level with medications available is good but few are completely satisfied and 26% are unsatisfied. • The tablet form of this medication addresses many issues that people who are currently taking other biologics face. • The new formulation is an opportunity for those who cannot tolerate NSAIDs. • The new formulation is an opportunity for the 20% of people who have not responded to other biologics and is the only one currently considered for non radiographic axial spondyloarthritis.

Thank you for your time.

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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)

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135604

Completed 27 July 2022
Updated 9 September 2022

CONTAINS [redacted] AND [redacted] DATA

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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Sarah Donegan	Critical appraisal of the statistical evidence
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Ashley Marsden	Critical appraisal of the company submission
Nicola Goodson	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

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.

7 REFERENCES

1. National Institute for Health and Care Excellence. Upadacitinib for treating active non-radiographic axial spondyloarthritis. Final scope. Published 10 March 2022; Available from: https://www.nice.org.uk/guidance/gid-ta10908/documents/final-scope. Accessed 24 May 2022.
2. Joo W, Almario CV, Ishimori M, Park Y, Jusufagic A, Noah B*, et al.* Examining treatment decision-making among patients with axial spondyloarthritis: insights from a conjoint analysis survey. ACR Open Rheumatol. 2020; 2:391-400.
3. AbbVie / HEOR Ltd. Expert interview report: Upadacitinib for the treatment of nr-axSpA. Data on file. 2022.
4. Michelena X, López-Medina C, Marzo-Ortega H. Non-radiographic versus radiographic axSpA: what's in a name? Rheumatology (Oxford). 2020; 59:iv18-iv24.
5. Novartis Europharm Ltd. Cosentyx. Annex I Summary of product characteristics. Published 24 June 2022; Available from: https://www.ema.europa.eu/en/documents/product-information/cosentyx-epar-product-information_en.pdf. Accessed 27 June 2022.
6. AbbVie. RINVOQ. Annex 1 Summary of product characteristics. Published 8 June 2022; Available from: https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf. Accessed 20 June 2022.
7. Eli Lilly and Company Ltd. Taltz. Annex I Summary of product characteristics. Published 9 February 2022; Available from: https://www.ema.europa.eu/en/documents/product-information/taltz-epar-product-information_en.pdf. Accessed 20 June 2022.
8. DRUGBANK Online. Upadacitinib. Published 26 June 2022; Available from: https://go.drugbank.com/drugs/DB15091. Accessed 27 June 2022.
9. DRUGBANK Online. Ixekizumab. Published 3 June 2022; Available from: https://go.drugbank.com/drugs/DB11569. Accessed 27 June 2022.
10. DRUGBANK Online. Secukinumab. Published 3 June 2022; Available from: https://go.drugbank.com/drugs/DB09029. Accessed 27 June 2022.
11. National Institute for Health and Care Excellence. Ixekizumab for treating axial spondyloarthritis. Technology appraisal guidance [TA718]. Published: 21 July 2021. Available from: https://www.nice.org.uk/guidance/ta718/chapter/1-Recommendations. Accessed 26 July 2022.
12. National Institute for Health and Care Excellence. Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors. Technology appraisal guidance [TA407]. Published: 28 September 2016. Available from: https://www.nice.org.uk/guidance/ta407. Accessed 12 July 2022.
13. National Institute for Health and Care Excellence. Secukinumab for treating non-radiographic axial spondyloarthritis. Technology appraisal guidance [TA719]. Published: 21 July 2021. Available from: https://www.nice.org.uk/guidance/ta719/chapter/1-Recommendations. Accessed 26 July 2022.
14. National Institute for Health and Care Excellence. Upadacitinib for treating active ankylosing spondylitis [ID3848]. Published 29 March 2022. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10735. Accessed 12 July 2022.
15. AbbVie. Clinical study report: M19-944. A Phase 3 randomized, placebo-controlled, double-blind program to evaluate efficacy and safety of upadacitinib in adult subjects with axial spondyloarthritis followed by a remission-withdrawal period. Data on file. 2021.
16. Deodhar A, Van den Bosch F, Poddubnyy D, Maksymowych WP, van der Heijde D, Kim TH*, et al.* Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis (SELECT-AXIS 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2022; 400:369-79.

17. Deodhar A, van der Heijde D, Gensler LS, Kim TH, Maksymowych WP, Østergaard M*, et al.* Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. Lancet. 2020; 395:53-64.
18. Deodhar A, Blanco R, Dokoupilová E, Hall S, Kameda H, Kivitz AJ*, et al.* Improvement of signs and symptoms of nonradiographic axial spondyloarthritis in patients treated with secukinumab: primary results of a randomized, placebo-controlled phase III study. Arthritis Rheumatol. 2021; 73:110-20.
19. Poddubnyy D JX PC, Russ H, Schymura Y, Liu-Leage S, Haschemi Nassab M, Dudler J,. Achievement of low disease activity according to BASDAI with ixekizumab in patients with axial spondyloarthritis: 16-week results from the COAST trials [abstract]. Arthritis Rheumatol. 2020. 72 (suppl 10). Available from: https://acrabstracts.org/abstract/achievement-of-low-disease-activity-according-to-basdai-with-ixekizumab-in-patients-with-axial-spondyloarthritis-16-week-results-from-the-coast-trials/. Accessed 11 July 2022.
20. Deodhar A, Mease P, Rahman P, Navarro-Compán V, Marzo-Ortega H, Hunter T*, et al.* Ixekizumab improves patient-reported outcomes in non-radiographic axial spondyloarthritis: results from the COAST-X trial. Rheumatol Ther. 2021; 8:135-50.
21. Marzo-Ortega H DA BR, Kameda H, Kivitz A, Poddubnyy D, Magrey M, Wang J, Haemmerle S, Shete A, Braun J. Secukinumab improves pain, morning stiffness, fatigue and physical function in tumor necrosis factor inhibitor-naïve patients with non-radiographic axial spondyloarthritis: Results from a randomized controlled Phase III study [abstract]. Arthritis Rheumatol. 2020. 72 (suppl 10). Available from: https://acrabstracts.org/abstract/secukinumab-improves-pain-morning-stiffness-fatigue-and-physical-function-in-tumor-necrosis-factor-inhibitor-naive-patients-with-non-radiographic-axial-spondyloarthritis-results-from-a-randomized-c/. Accessed 11 July 2022.
22. Hamilton L, Barkham N, Bhalla A, Brittain R, Cook D, Jones G*, et al.* BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. Rheumatology (Oxford). 2017; 56:313-6.
23. National Institute for Health and Care Excellence. TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Technology appraisal guidance [TA383]. Published: 01 February 2016. Available from: https://www.nice.org.uk/guidance/ta383. Accessed 11 July 2022.
24. National Institute for Health and Care Excellence. Spondyloarthritis in over 16s: diagnosis and management NICE guideline [NG65]. Published: 28 February 2017. Last updated: 02 June 2017. Available from: https://www.nice.org.uk/guidance/ng65. Accessed 7 July 2022.
25. Medicines & Healthcare products Regulatory Agency. Tofacitinib (Xeljanz▼): new measures to minimise risk of major adverse cardiovascular events and malignancies. Published 6 October 2021. Available from: https://www.gov.uk/drug-safety-update/tofacitinib-xeljanzv-new-measures-to-minimise-risk-of-major-adverse-cardiovascular-events-and-malignancies. Accessed 25 July 2022.
26. European Medicines Agency. Rinvoq: Pending EC decision. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/rinvoq-2. Accessed 25 Jul 2022.
27. Deodhar A, Gensler LS, Kay J, Maksymowych WP, Haroon N, Landewé R*, et al.* A fifty-two-week, randomized, placebo-controlled trial of certolizumab pegol in nonradiographic axial spondyloarthritis. Arthritis Rheumatol. 2019; 71:1101-11.
28. Dougados M, van der Heijde D, Sieper J, Braun J, Maksymowych WP, Citera G*, et al.* Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2014; 66:2091-102.
29. Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H*, et al.* Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined

sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Arthritis Rheumatol. 2008; 58:1981-91.
30. Landewé R, Braun J, Deodhar A, Dougados M, Maksymowych WP, Mease PJ*, et al.* Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis. 2014; 73:39-47.
31. Landewé RB, Sieper J, Mease P, Inman RD, Lambert RG, Deodhar A*, et al.* Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. Lancet. 2018; 392:134-44.
32. Pfizer. A multicenter open-label study of etanercept withdrawal and retreatment in subjects with non-radiographic axial spondyloarthritis who achieved adequate 24 week response. Published 16 June 2020; Available from: https://clinicaltrials.gov/ct2/show/NCT02509026. Accessed 6 June 2022.
33. Proft F, Weiss A, Torgutalp M, Protopopov M, Rodriguez VR, Haibel H*, et al.* Sustained clinical response and safety of etanercept in patients with early axial spondyloarthritis: 10-year results of the ESTHER trial. Ther Adv Musculoskel Dis. 2021; 13:1-14.
34. Sieper J, van der Heijde D, Dougados M, Maksymowych WP, Scott BB, Boice JA*, et al.* A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol. 2015; 67:2702-12.
35. Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA*, et al.* Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis. 2013; 72:815-22.
36. Centre for Reviews and Dissemination. Systematic Reviews. CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination, University of York, 2009. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed 11 July 2022.
37. AbbVie. Protocol for clinical study M19-944 Axial spondyloarthritis: evaluation of upadacitinib in adult subjects – SELECT-AXIS 2. Data on file. 2021.
38. van der Heijde D, Cheng-Chung Wei J, Dougados M, Mease P, Deodhar A, Maksymowych WP*, et al.* Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. Lancet. 2018; 392:2441-51.
39. Deodhar A, Poddubnyy D, Pacheco-Tena C, Salvarani C, Lespessailles E, Rahman P*, et al.* Efficacy and safety of ixekizumab in the treatment of radiographic axial spondyloarthritis: sixteen-week results from a phase III randomized, double-blind, placebo-controlled trial in patients with prior inadequate response to or intolerance of tumor necrosis factor inhibitors. Arthritis Rheumatol. 2019; 71:599-611.
40. Braun J, Baraliakos X, Deodhar A, Baeten D, Sieper J, Emery P*, et al.* Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. Ann Rheum Dis. 2017; 76:1070.
41. Sieper J, Deodhar A, Marzo-Ortega H, Aelion JA, Blanco R, Jui-Cheng T*, et al.* Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: results from the MEASURE 2 Study. Ann Rheum Dis. 2017; 76:571.
42. Altman DG, Bland JM. Absence of evidence is not evidence of absence. BMJ. 1995; 311:485.

43. British National Formulary. Ixekizumab. Published 26 May 2022; Available from: https://bnf.nice.org.uk/drugs/ixekizumab/#indications-and-dose. Accessed 15 June 2022.
44. British National Formulary. Secukinumab. Published 26 May 2022; Available from: https://bnf.nice.org.uk/drugs/secukinumab/#indications-and-dose. Accessed 15 June 2022.
45. Curtis L BA. Unit Costs of Health and Social Care 2019. Personal Social Services Research Unit, University of Kent, UK. 2019; Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/. Accessed 11 July 2022.
46. National institute for Health and Care Excellence Decision Support Unit. NICE DSU Technical Support Document 2: a generalised linear modelling framework or pairwise and network meta-analysis of randomised controlled trials. Published April 2014. Available from: https://www.ncbi.nlm.nih.gov/books/NBK310366/pdf/Bookshelf_NBK310366.pdf. Accessed 23 June 2022.
47. National Institute for Health and Care Excellence Decision Support Unit. NICE DSU Technical Support Document 3: heterogeneity: subgroups, meta-regression, bias and bias-adjustment. Published April 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK395886/pdf/Bookshelf_NBK395886.pdf. Accessed 23 June 2022.
48. National Institute for Health and Care Excellence Decision Support Unit. NICE DSU Technical Support Document 4: inconsistency in networks of evidence based on randomised controlled trials. Published April 2014. Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD4-Inconsistency.final_.15April2014.pdf. Accessed 23 June 2022.
49. Harvey LA. Statistical testing for baseline differences between randomised groups is not meaningful. Spinal Cord. 2018; 56:919.
50. de Boer MR, Waterlander WE, Kuijper LD, Steenhuis IH, Twisk JW. Testing for baseline differences in randomized controlled trials: an unhealthy research behavior that is hard to eradicate. Int J Behav Nutr Phys Act. 2015; 12:4.
51. Chen H, Lu Y, Slye N. Testing for baseline differences in clinical trials. 2020. 2020; 7:4.

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

Single Technology Appraisal

Upadacitinib for treating active non-radiographic axial spondyloarthritis [ID3958]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 31 August 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Updates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2 Page 11 Table 2 **“**Marketing authorisation is being sought for the treatment of active nr-axSpA in adult patients with OSI who have responded inadequately to NSAIDs”	“Indicated for the treatment of active nr-axSpA in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).”	Upadacitinib for the treatment of nr-axSpA has received marketing authorisation. The text has been updated to reflect this.	Updated table
Section 2.2 Page 11 Table 2 “Rheumatoid arthritis Psoriatic arthritis Atopic dermatitis”	“Rheumatoid arthritis Psoriatic arthritis Atopic dermatitis Ulcerative colitis”	Upadacitinib is now indicated for the treatment of ulcerative colitis, the text has been updated to reflect this.	Updated table

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2 Page 12 Table 3 "ID3848: Cost Comparison in development with the suggested remit to appraise the clinical and cost effectiveness of upadacitinib within its marketing authorisation for treatment of active AS in adults who have responded inadequately to conventional therapy Guidance is expected 17 August 2022"	"ID3848: Upadacitinib is recommended as an option for treating active ankylosing spondylitis that is not controlled well enough with conventional therapy in adults, only if: tumour necrosis factor (TNF)-alpha inhibitors are not suitable or do not control the condition well enough, and the company provides upadacitinib according to the commercial arrangement"	The draft guidance was published on 17 August 2022,[3] therefore, the table should be updated to reflect the latest information.	Updated table
Section 2.3 Page 12 "SELECT-AXIS 2 trial results are yet to be published, however, the company has provided data from the clinical study report.[4]"	"SELECT-AXIS 2 trial results were not published at the time of the company submission, however, the company provided data from the clinical study report.[4] The trial result have since been published in Deodhar et al 2022.[5]"	The trial results have now been published in Deodhar et al. 2022,[5] therefore, the text has been amended to reflect this.	Updated text

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.5 Page 16 "It is unknown how many patients were not able to tolerate or achieve an adequate response to TNFα inhibitors."	"[redacted] were not able to tolerate or achieve an adequate response to TNFα inhibitors."	[redacted] of treatment naïve patients were not able to tolerate or achieve an adequate response to TNFα inhibitors. The text has been updated to reflect this.	[redacted] is the proportion of patients in the SELECT-AXIS 2 trial who had previously received a bDMARD. However, the text in the EAG report refers to all of the studies included in the NMAs. No change made to text
Section 3.6.2 Page 17 "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 for AS for longer than ixekizumab."	"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."	Further clarification required that secukinumab has been available longer than ixekizumab in AS but for nr-axSpA both secukinumab and ixekizumab have been indicated since July 2021. The text has been updated to clarify this.	Updated text

Issue 2 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1 Page 10 "(CS, p16 and pp18-19)"	"pp18-19" should be "p18-19"	Typographical error	Text is from p18 to p19, hence "pp". No change made to text
Section 3.3 Page 15 "The company highlights (CS, p41) that these are also the key clinical outcomes recommended by the British Society of Rheumatology guidelines[21] to assess nr-axSpA activity."	"The company highlights (CS, p48) that these are also the key clinical outcomes recommended by the British Society of Rheumatology guidelines[21] to assess nr-axSpA activity."	Typographical error. Reference to BSR guidelines is mentioned on page 48 not 41.	Thank you for identifying this error, text amended
Section 4.3.1 Page 20 "The company adopted a Bayesian NMA approach (CS, Appendix K, Section 2).	"Section 2" should be "Section 4"	Incorrect section reported	Thank you for identifying this error, text amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.3.1 Page 20 "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 regression coefficients that were not statistically significant with random effects (RE) and risk-adjusted FE and RE models (CS, Appendix K, Section 5.3)."	"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)."	Missing word "of"	Thank you for identifying this error, text amended
Section 4.2.4 Page 19 "Pre-specified subgroup analyses for AS disease activity score 40 (ASDAS40) are presented in the CS (Appendix J, Section B.1.4)."	"AS disease activity score 40 (ASDAS40)" should be "ASAS40"	Incorrect outcome reported	Thank you for identifying this error, text amended
Section 4.6 Page 26 "However, the proportion of patients reporting any AE by Week 14 was [redacted] the upadacitinib ([redacted]) and placebo arms ([redacted]).	"[redacted]" should be "[redacted]"	Typographical error	Thank you for identifying this error, text amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.7 Page 28 **“**stated that clinical advice to the company is that upadacitinib has comparable health benefits to ixekizumab and secukinumab”.	This bullet point needs to be removed from this section.	The clinical advice provided to the company supports the cost-comparison approach, however this specific point was not included by the company as part of the response to Clarification Question A1.	It is stated in response to Clarification Question A1 (bottom of p2): “Furthermore, clinical expert agreed that upadacitinib has comparable health benefits to ixekizumab and secukinumab.” No change made to text
Section 8.2.1 Page 39 Table 10 “Clinical advice to the EAG is that treatment effect modifiers identified appear to be appropriate is that treatment effect modifiers identified appear to be appropriate”	“Clinical advice to the EAG is that treatment effect modifiers identified appear to be appropriate”	Repetition	Thank you for identifying this error, text amended
Section 8.2.4 Page 42 Table 11 “[redacted]”	“[redacted]” should be “[redacted])”	Missing end bracket	Thank you for identifying this error, table amended
Section 8.2.4 Page 42 Table 12 “[redacted]”	“[redacted]” should be “[redacted]”	Typographical error. The lower credible interval reported for BASDAI CFB for Placebo is from NMA 3 not NMA 1 as stated in the table title.	Thank you for identifying this error, table amended

Issue 3 Confidential marking

The EAG thanks the company for highlighting the changes in confidential marking below. The EAG has implemented all the amended marking.

Location of incorrect marking	Description of incorrect marking	Amended marking
General comment: Due to the recent publication of the SELECT-AXIS 2 trial results,[5] the academic in confidence marking for some of the data presented in the EAG report should be updated, as described below.		
Section 1.2 Page 8 "SELECT-AXIS 2 trial ([redacted], [redacted])"	This data is now published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer required.	"SELECT-AXIS 2 trial (210/313, 67.1%)"
Section 1.2 Page 9 "After a minimum of 52 weeks, there were a small number of patients who developed uveitis events in all three trials (SELECT-AXIS 2: [redacted], [redacted]; COAST-X: 3/198, 1.5%; PREVENT: 9/369, 2.4%)."	This data is now published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer required.	"After a minimum of 14 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%)."
Section 1.2 Page 9 "[redacted] patients in the SELECT-AXIS 2 trial"	This data is now published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer required.	"No patients in the SELECT-AXIS 2 trial at week 14"
Section 4.2.3 Page 19 **"**A statistically significant greater proportion of patients treated with upadacitinib ([redacted], [redacted]) achieved ASAS40 than patients treated with placebo ([redacted], [redacted]) (CS, Table 12)."	This data is now published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer required.	"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)."

Location of incorrect marking	Description of incorrect marking	Amended marking
Section 4.4.3 Page 22 "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 ([redacted], [redacted]), the COAST-X trial (0/303) and the PREVENT trial (54/555, 9.7%) were different."	This data is now published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer required.	"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."
Section 4.4.3 Page 23 **"**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 ([redacted] to [redacted] years and [redacted] to [redacted] years, respectively) and COAST-X trials (3.10 to 4.20 years and 10.10 to 11.30 years, respectively."	This data is now published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer required.	"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."
Section 4.4.3 Page 23 "the proportion of patients who were human leukocyte antigen B27 (HLA-B27) positive was lower in the SELECT-AXIS 2 trial ([redacted], [redacted]) than in the COAST-X (221/303, 72.9%) and PREVENT trials (382/555, 68.8%)."	This data is now published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer required.	"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%)."

Location of incorrect marking	Description of incorrect marking	Amended marking
Section 4.4.3 Page 23 "the proportion of patients who showed sacroiliac joint inflammation on MRI was lower in the SELECT-AXIS 2 trial ([redacted], [redacted]) than in the COAST-X (217/303, 71.6%) and PREVENT trials (405/555, 73.0%)."	This data is now published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer required.	"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%)."
Section 4.4.3 Page 23 "the proportion of patients who received concomitant NSAIDs was lower in the SELECT-AXIS 2 trial ([redacted], [redacted]) than in the COAST-X (272/303, 89.8%) and PREVENT trials (463/555, 83.4%)."	This data is now published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer required.	"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%)."
Section 4.6 Page 26 "A [redacted] proportion of patients reported any AE by Week 14 in the SELECT-AXIS 2 trial ([redacted], [redacted]) 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 [redacted] the upadacitinib ([redacted], [redacted]) and placebo arms ([redacted], [redacted])."	This data is now published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer required.	"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, 42.9%)."
Section 4.6 Page 26 Table 5	This data is now published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer	"

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<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th></tr>
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<tr><td>Nasopharyngitis, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Injection site reaction, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Headache, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Upper respiratory tract infection, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Hypertension, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Diarrhoea, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Neutropenia, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>IBD, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
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<tr><td>Nasopharyngitis, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Injection site reaction, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Headache, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Upper respiratory tract infection, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Hypertension, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Diarrhoea, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Neutropenia, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
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SELECT-AXIS 2 data
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<td>Some of the baseline characteristics data for SELECT-AXIS 2 presented in Table 14 has now been published in Deodhar et al. 2022,[5] therefore, confidential marking is no longer required for this data.</td>
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<table><tr><th></th><th colspan="2">SELECT-AXIS 2</th></tr><tr><th></th><th>PBO (n=157)</th><th>UPA (n=156)</th></tr><tr><td>Age, years, mean (SE)</td><td>42.50 [redacted]</td><td>41.60[redacted]</td></tr><tr><td>Male, n (%)</td><td>63 (40.1)</td><td>67 (42.9)</td></tr><tr><td>Diagnosis duration (years), mean (SE)</td><td>4.35 [redacted]</td><td>4.55 [redacted]</td></tr><tr><td>Symptoms duration (years), mean (SE)</td><td>9.20 [redacted]</td><td>9.00 [redacted]</td></tr><tr><td>CRP (mg/L), mean (SE)</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>CRP+, n (%)</td><td>84 (53.5)</td><td>99 (63.5)</td></tr><tr><td>HLA-B27, n (%)</td><td>93 (59.2)</td><td>90 (57.7)</td></tr><tr><td>BASFI (0-10), mean (SE)</td><td>5.99 [redacted]</td><td>5.89 [redacted]</td></tr><tr><td>BASDAI (0-10), mean (SE)</td><td>6.91 [redacted]</td><td>6.82 [redacted]</td></tr></table></td>
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<tr><td>Concomitant csDMARD, n (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
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SELECT-AXIS 2 data</td>
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<tr><td>%*</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>ASAS40</td><td></td><td></td></tr>
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<tr><td>N responded</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Proportion*</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>ASASPR</td><td></td><td></td></tr>
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<tr><td>N responded</td><td>69</td><td>104</td></tr>
<tr><td>%*</td><td>43.9%</td><td>66.7%</td></tr>
<tr><td>ASAS40</td><td></td><td></td></tr>
<tr><td>N assessed</td><td>157</td><td>156</td></tr>
<tr><td>N responded</td><td>35</td><td>70</td></tr>
<tr><td>Proportion*</td><td>22.3%</td><td>44.9%</td></tr>
<tr><td>ASASPR</td><td></td><td></td></tr>
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<tr><td>N responded</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Proportion*</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>BASDAI50</td><td></td><td></td></tr>
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<tr><td>N responded</td><td>35</td><td>66</td></tr>
<tr><td>Proportion*</td><td>22.3%</td><td>42.3%</td></tr>
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Location of incorrect marking			Description of incorrect marking	Amended marking		
N assessed	[redacted]	[redacted]		**BASDAI CFB**		
N responded	[redacted]	[redacted]		Endpoint N	[redacted]	[redacted]
Proportion*	[redacted]	[redacted]		Mean (SE)	[redacted]	[redacted]
BASDAI CFB				**BASFI CFB**		
Endpoint N	[redacted]	[redacted]		Endpoint N	156	154
Mean (SE)	[redacted]	[redacted]		Mean (SE)	-1.470 [redacted]	-2.610 [redacted]
BASFI CFB				**Total Back Pain CFB**		
Endpoint N	[redacted]	[redacted]		Endpoint N	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]		Mean (SE)	-2.000 [redacted]	-2.910 [redacted]
Total Back Pain CFB						
Endpoint N	[redacted]	[redacted]				
Mean (SE)	[redacted]	[redacted]				

(Please add further lines to the table as necessary)

References

1. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2022. Available at: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 [Accessed 30 August 2022].
2. National Institute for Health and Care Excellence. TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis Technology appraisal guidance [TA383]. 2016. Available at: https://www.nice.org.uk/guidance/ta383/resources/tnfalpha-inhibitors-for-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-pdf-82602848027077 [Accessed 30 August 2022].
3. National Institute for Health and Care Excellence. Final appraisal document: Upadacitinib for treating active ankylosing spondylitis [ID3848]. 2022. Available at: https://www.nice.org.uk/guidance/gid-ta10735/documents/final-appraisal-determination-document [Accessed 25 August 2022].
4. AbbVie. Clinical study report: M19-944. A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of Upadacitinib in Adult Subjects with Axial Spondyloarthritis Followed by a Remission-Withdrawal Period. Data on file. 2021.
5. Deodhar A, Van den Bosch F, Poddubnyy D, et al. Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis (SELECT-AXIS 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2022;400(10349):369-79.

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