NICE National Institute for Health and Care Excellence

FAST TRACK APPRAISAL (FTA)

Upadacitinib for treating active ankylosing spondylitis [ID3848]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Upadacitinib for treating active ankylosing spondylitis [ID3848]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder** **list** are available on the NICE website.

1. **Company cost comparison** from AbbVie[1]

2. **Clarification letters**
   - Company response to NICE's request for clarification

3. **Patient group, professional group and NHS organisation submission** from:
   a. National Axial Spondyloarthritis Society
   b. British Society for Rheumatology (endorsed by the Royal College of Physicians)

4. **Expert personal perspectives** from:
   a. Dr Raj Sengupta – clinical expert, nominated by AbbVie
   b. Frances Reid – patient expert, nominated by National Axial Spondyloarthritis Society
   c. Thomas Prior – patient expert, nominated by National Axial Spondyloarthritis Society

5. **Evidence Review Group report** prepared by York Centre for Reviews and Dissemination

6. **Evidence Review Group – factual accuracy check**

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

[1] Please note that during the scrutiny process it was decided that the most appropriate comparators for upadactinib in the FTA process were the IL-17 inhibitors, secukinumab and ixekizumab. As such the appropriate population is now the bDMARD experienced population. The original submission document has been included for information but all comparisons with and references to the bDMARD-naïve population (in the submissions or model) are no longer part of the decision problem for this FTA.

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Fast track appraisal: cost-comparison case

Upadacitinib for treating active ankylosing spondylitis [ID3848]

Document B

Company evidence submission

November 2021

File name	Version	Contains confidential information	Date
ID3848_Upadacitinib_AS_NICE_Document B_FINAL_[ACIC Redacted]	1.0	Yes	30/11/21

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List of abbreviations

Abbreviation	Definition
ADA40	Adalimumab 40 mg
AE	Adverse event
AS	Ankylosing spondylitis
ANCOVA	Analysis of covariance
ASAS	Assessment of ankylosing spondylitis
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 index
BASFI	Bath ankylosing spondylitis functional index
BASMI	Bath ankylosing spondylitis disease metrology index
bDMARD	Biologic disease modifying antirheumatic drug
BNF	British National Formulary
BSR	British Society of Rheumatology
CI	Confidence interval
CrI	Credible interval
CSR	Clinical study report
CZP 200/400	Certolizumab pegol 200/400 mg
DMARD	Disease modifying antirheumatic drug
EAM	Extra-articular manifestation
EMA	European Medicines Agency
ETN25/50	Etanercept 25/50 mg
GOL50/100	Golimumab 50/100 mg
hsCRP	High sensitivity C-reactive protein
IL-17	Interleukin 17
INF5	Infliximab 5 mg
IR	Inadequate responder

Abbreviation	Definition
ITC	Indirect treatment comparison
IXE80Q2W/Q4W	Ixekizumab 80 mg every two weeks/every four weeks
JAKs	Janus Kinases
LD	Loading dose
MASES	Maastricht ankylosing spondylitis enthesitis score
MI	Multiple imputation
MRI	Magnetic resonance imaging
mSASSS	Modified Stoke ankylosing spondylitis spine score
NA	Not applicable
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NRI	Non-responder imputation
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PBO	Placebo
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q2W	Every two weeks
Q4W	Every four weeks
QD	Once a day
QoL	Quality of life
SEC150/300	Secukinumab 150/300 mg
SmPC	Summary of product characteristics
SPARCC	Spondyloarthritis Research Consortium of Canada
STATs	Signal transducer and activator of transcription
TOF2/5/10	Tofacitinib 2/5/10 mg
TNFα	Tumour necrosis factor α
TNFi	Tumour necrosis factor inhibitor
TYK	Tyrosine kinase
UPA15	Upadacitinib 15 mg
VAS	Visual analogue scale
WPAI	Work productivity and activity impairment questionnaire

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

B.1.1 Decision problem

B.1.1.1 Population

This submission addresses the full marketing authorisation for upadacitinib, indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.[1] Consistent with the NICE multiple technology appraisal (MTA) for tumour necrosis factor α (TNFα) inhibitors in the treatment of AS (TA383),[2] conventional therapy is considered to include non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. The decision problem addressed is consistent with the final NICE scope for this appraisal, as outlined in Table 1.

B.1.1.2 Comparators

B.1.1.2.1 NICE HTA Guidance

AbbVie are proposing that the appraisal of upadacitinib be considered under the NICE Fast Track Appraisal (FTA) process. The NICE user guide for FTA states that a cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in published technology appraisal guidance for the same indication.[3]

Criteria for the selection of an appropriate comparator state that the selected comparator must fulfil the following:

- It adequately represents the NICE recommended treatments as a whole both in terms of costs and effects;
- It has significant market share;
- It is recommended in published NICE technology appraisal guidance for the same indication.

B.1.1.2.2 Comparable health benefits

Considering the initial requirement of similar clinical efficacy to meet the criteria for cost comparison, a series of indirect comparisons were conducted to estimate the relative efficacy of upadacitinib against the full range of comparators specified in the final scope (including

TNFα and IL-17A inhibitors). Evidence from the indirect comparisons demonstrates that upadacitinib has similar efficacy to all potential comparators (Section B.3.9).

B.1.1.2.3 NICE recommended treatments and final comparators

A clinical need exists for therapies that have different mechanisms of action to currently available treatments for AS. This is demonstrated by the NICE recommendation for the IL-17A inhibitor, secukinumab for the full active AS population as an alternative to TNFα inhibitors (TNFi), and secukinumab's significant market share across both biologic-naïve and experienced patients, [redacted]% and [redacted]% in Q2 2021, respectively. These figures are estimates based on market research conducted in 2021, sampling a select number of clinicians treating AS patients. Although ixekizumab only recently has been recommended by NICE in biologic experienced AS patients, its market share is expected to increase in due course.

Clinician feedback indicated that the clinical decision would centre on whether to use IL-17A inhibitors or upadacitinib, and therefore, upadacitinib would be used in the same place in the treatment pathway as IL-17A inhibitors.[4] It is especially important to have an alternative mechanism of action available for patients with extra-articular manifestations, such as inflammatory bowel disease (IBD), who are contra-indicated for IL-17A inhibitors.[5] As the first oral therapy for the treatment of AS, clinicians also highlighted the benefit of an alternative mode of administration within this patient population (Section B.1.3.4)

Hence, this submission primarily compares upadacitinib against the IL-17A inhibitors, secukinumab and ixekizumab, utilising a cost-minimisation approach. Secukinumab is recommended for patients with active AS, after treatment with NSAIDs or TNFi,[6] whereas ixekizumab, the IL-17A therapy most recently assessed by NICE guidance (TA718),[7] is recommended for biologic-experienced AS patients. This is particularly relevant considering the potential data limitations for secukinumab in biologic-experienced AS patients,[5] which will be explained in more detail Section B.3.9.1. Therefore, both secukinumab and ixekizumab are recommended in published NICE technology appraisal guidance for the same indication and population as upadacitinib. Secukinumab and ixekizumab were previously demonstrated to be cost-effective in their respective positions in the treatment pathway,[6,7] and therefore, it is sufficient to compare upadacitinib to these comparators alone.

In conclusion, based on criteria established by NICE for selecting appropriate comparators under an FTA cost-comparison route and clinical feedback, both IL-17A therapies can be deemed the most relevant comparators, as summarised below:

- Secukinumab and ixekizumab represent the NICE recommended treatments for this population and indication, and have previously demonstrated clinical efficacy and cost-effectiveness.[6,7]
- IL-17A inhibitors have a significant market share in treatment-naïve and experienced populations, Secukinumab had a market share of [redacted]% and [redacted]% in bDMARD-naïve and bDMARD-experienced patients, respectively in September 2021,
- Upadacitinib has comparable clinical efficacy to secukinumab and ixekizumab, as demonstrated by the NMA in Section 3.9, and was confirmed by UK clinicians to be an alternative therapeutic option to IL-17A inhibitors, for both the bDMARD-naïve and bDMARD-experienced populations.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from NICE
Population	Treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.	Treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy (bDMARD-naïve and bDMARD experienced).	As per NICE scope
Intervention	Upadacitinib 15mg	Upadacitinib 15 mg	As per NICE scope
Comparators	TNFα inhibitors including: • Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Infliximab IL-17A inhibitors: • Secukinumab • Ixekizumab	TNFα inhibitors including: • Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Infliximab IL-17A inhibitors: • Secukinumab • Ixekizumab	Clinical effectiveness evidence is provided versus all specified comparators in order to demonstrate that upadacitinib has similar efficacy compared with all potential comparators. Cost-comparison evidence is provided versus secukinumab and ixekizumab, aligned with criteria established by NICE for selecting appropriate comparators under an FTA cost-comparison route. The positioning of upadacitinib is anticipated to align with secukinumab and ixekizumab, which have previously demonstrated similar clinical efficacy and cost-effectiveness. Based on this rationale, secukinumab and ixekizumab can be considered the most appropriate comparators for this submission.
Outcomes	The outcome measures to be considered include: • Disease activity • Functional capacity • Disease progression • Pain	• Disease activity: ASAS40; BASDAI 50; BASDAI change from baseline (CFB); ASAS partial remission; ASDAS CRP; hsCRP CFB; patient's global	As per NICE scope

	• 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	assessment of disease activity (PtGA) • Functional capacity: BASFI CFB; BASMI • Disease progression: mSASSS, MRI outcomes • Pain: captured by ASAS and BASDAI criteria, which include total back pain: spinal pain including neck, back and hips and nocturnal back pain: peripheral joint pain and global assessment. • Peripheral symptoms, including enthesitis, peripheral arthritis and dactylitis: MASES • Symptoms of extra-articular manifestations including uveitis, inflammatory bowel disease and psoriasis • Adverse events • Health-related quality of life: ASQoL, WPAI	
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	• Cost comparison is provided • 5 year time horizon, with results disaggregated by year • The perspective of the NHS and PSS is used • Patient access schemes for upadacitinib is accounted for	A cost comparison has been considered appropriate, based on evidence that upadacitinib 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. The company submission focuses on secukinumab and ixekizumab for the cost-comparison analysis, as outlined above.

	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 considered. The availability of any managed access arrangement for the intervention will be considered.		Any major differences in total cost are expected to be due to differences in drug acquisition price. Therefore, evaluation of annual total costs is likely the most pertinent comparison, however, results for a five-year time horizon (disaggregated by year) have been provided for completeness.
Subgroups to be considered	Not specified	No subgroup analyses are presented for the economic analysis in line with the NICE scope. To account for the full active AS population separate analyses have been conducted for the bDMARD-naïve and bDMARD-IR populations.	Not applicable
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 appraised

A description of the technology being appraised (upadacitinib [RINVOQ®]) is provided in Table 2. The Summary of Product Characteristics and European Public Assessment Report are attached in Appendix A.

Table 2. Technology being appraised

UK approved name and brand name	Upadacitinib RINVOQ®
Mechanism of action	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 especially important in inflammatory cytokine signals. 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.[1]
Marketing authorisation/CE mark status	Upadacitinib received marketing authorisation for this indication via the European Medicines Agency (EMA) in January 2021 and is therefore licensed for marketing in the European Union.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Upadacitinib is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy. Upadacitinib also holds marketing authorisations for rheumatoid arthritis, atopic dermatitis (adult and adolescent) and psoriatic arthritis, which are not the subject of this submission.[1]
Method of administration and dosage	Oral, 15 mg prolonged-release tablet once-daily
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.[1] Estimates are based on patients receiving one tablet per day for 365.25 days per year.
Patient access scheme (if applicable)	Upadacitinib (RINVOQ®) 15 mg tablets Unit price: [redacted] Pack of 28 tablets: [redacted] Annual maintenance treatment at 15 mg: [redacted] Treatment discontinuation is 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.[1] Estimates are based on patients receiving one tablet per day for 365.25 days per year.
EMA: European Medicines Agency; JAK: Janus kinase; STATs: signal transducers and activators of transcription; TYK: non-receptor tyrosine-protein kinase. Source: EMA RINVOQ® Summary of Product Characteristics[1]	

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

B.1.3.1 Disease overview

Ankylosing spondylitis (AS) is the most common and severe phenotype of axial spondyloarthritis (axSpA), a clinically heterogeneous group of overlapping inflammatory rheumatic diseases. It is a progressive, irreversible arthritis characterised by inflammation in the spine and sacroiliac joints. The resulting back pain and stiffness have a considerable impact on patients' physical ability, pain, quality of life (QoL) and social functioning.[8]

If there is radiographic evidence of inflammation, the disease is classified as AS (also known as radiographic axSpA). If there is no radiographic evidence of inflammation, but there are other objective signs of inflammation (such as elevated C-reactive protein [CRP] or evidence on magnetic resonance imaging [MRI]) the disease is classified as non-radiographic axSpA (nr-axSpA).[9,10] Approximately 10–40% of patients with nr-axSpA progress to AS over 2–10 years.[11]

AS is associated with the formation of new bone (osteoproliferation) resulting in bone fusion and sclerosis of the sacroiliac joints and spine. These structural changes in the sacroiliac joints cause chronic, severe back pain and morning stiffness usually lasting a few hours. Additionally, bone fusion results in skeletal/postural changes, which lead to physical impairment and potential immobility. This physical impairment can affect a patient's ability to carry out daily activities, such as walking and working, which have a direct effect on social, psychological and QoL decline.[8] The early age of onset, which on average occurs between 20-30 years,[12] is a critical factor affecting QoL, as AS manifests at a crucial age of educational, professional and social development.[13]

B.1.3.2 Epidemiology

The exact prevalence of AS in the UK is unknown. A UK cross-sectional cohort study of 505 people found a prevalence of axSpA of 0.66%, using modified New York criteria in an adult primary care population with low back pain and 0.15% in the general adult primary care population.[14]

Based on population estimates in 2020, there are between 33,398 and 153,632 adults with AS in the UK.[15] However, it is believed that these figures may underestimate the real prevalence of AS, partly due to an average diagnostic delay of 8.57 years,[16-18] which was recently highlighted in the NASS review: A Gold Standard Time to diagnosis.[18]

The typical age of onset of AS is between 17-35 years of age, with 90-95% of patients with AS diagnosed before the age of 45.[19,20] Patients with AS are of working age and are essential contributors to the workforce and the economy.

B.1.3.3 Current pathway of care

Many treatments for AS aim to delay the progression of the disease by reducing damage to the joints and spine through suppression of inflammation. Current treatment includes a combination of pharmacological and non-pharmacological approaches. Non-pharmacological interventions include patient education, lifestyle choices and physical therapy.[13] In addition, contact with patient support groups, such as the National Axial Spondyloarthritis Society (NASS), should be encouraged as this has the potential to increase motivation and compliance to treatment in a chronic condition such as AS.

The initial pharmacological treatments for symptomatic, active AS are continuous NSAIDs, which are effective in controlling pain and stiffness, as well as maintaining mobility. In addition to managing symptoms, NSAIDs also reduce inflammation.[21] Treatment with NSAIDs, alongside physiotherapy, is classified as 'conventional therapy' in all previous NICE appraisals. Despite their widespread use and efficacy, continuous treatment with NSAIDs can be associated with hypertension, abdominal pain and cardiovascular and renal related side-effects.[22-24] Furthermore, gastrointestinal symptoms, which include nausea, dyspepsia and diarrhoea occur in 10-60% of patients using NSAIDs.[25] Due to this profile, NSAIDs are only prescribed on-demand for short periods in other diseases. Therefore, despite their long-term efficacy in AS, the variety and frequency of side-effects limits their use in many patients. Similarly, as NSAIDs primarily operate by managing the symptoms of AS, rather than modifying radiographic disease progression, spinal and joint damage is ongoing while undergoing NSAID treatment.[26]

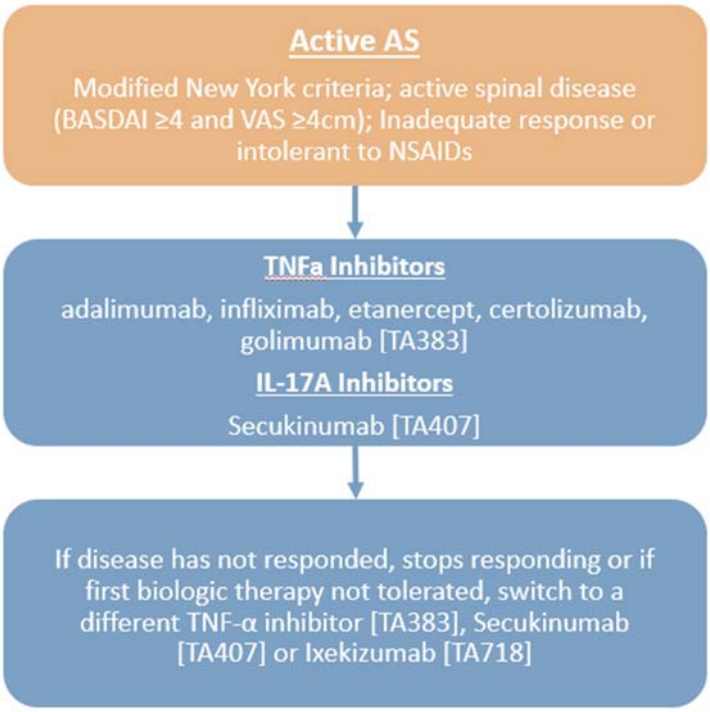
Biologic disease modifying anti-rheumatic drugs (bDMARDs) directly target the signalling pathways involved in AS pathogenesis, and therefore, also reduce disease progression.[27] TNFα inhibitors (TNFi) target TNFα to inhibit the downstream signalling pathways associated with inflammation and bone formation for the treatment of AS.[28] In 2016, the IL-17A inhibitor secukinumab was recommended by NICE for the treatment of active AS, offering another

treatment option for patients who have responded inadequately, or who cannot tolerate, conventional therapy or TNFα inhibitors.[6] A second IL-17A inhibitor, ixekizumab is also licensed for the treatment of active AS with inadequate response to TNFα inhibitors . An adequate response in AS treatment is considered by NICE to be a reduction of the BASDAI score to 50% of the pre-treatment value (BASDAI50) or by two units or more, together with a reduction of the spinal pain VAS by 2 cm or more.[2] NICE guidance states that bDMARDs, including TNFi and IL-17A inhibitors should be considered in all adult AS patients with persistently high disease activity (BASDAI score ≥4).[7,29]

The ASDAS inactive disease and ASAS partial remission criteria remain the only formally defined remission criteria in AS. The ASDAS composite index allows for the evaluation of disease severity ranging from inactive disease to very high disease depending on the score that is achieved. The ASDAS inactive disease criteria is met when a score of <1.3 is achieved in the following patient reported assessments: back pain, duration of morning stiffness, peripheral joint pain and/or swelling, general well-being, serological markers of inflammation and erythrocyte sedimentation rate or C-reactive protein.

An advisory board comprising of clinicians specialising in the treatment of AS in the NHS in England was conducted by AbbVie to elicit information on the current patient pathway.[4] It was confirmed during the meeting that in most bDMARD- naïve patients, clinicians would prescribe a TNFi over secukinumab, unless contra-indicated to TNFi. Currently, there are limited treatment options for patients with AS, as there are only two mechanisms of action available, which is especially limiting in patients contra-indicated to one or both current mechanisms (Section B.1.3.4). As discussed in Section B.1.1, upadacitinib is considered as an alternative therapy to IL-17A inhibitors during clinical decision making for AS patients in line with relevant NICE guidelines.

Figure 1. Treatment pathway for patients with active AS



AS: ankylosing spondylitis; BASDAI: Bath ankylosing spondylitis disease activity index; NSAIDs: non-steroidal anti-inflammatory drugs; TNFa: tumour necrosis factor alpha; VAS: visual analogue scale

B.1.3.4 Limitations in current treatment pathway

AS is a life-long, progressive condition that can lead to irreversible spinal deformities and a reduced QoL. There are currently several challenges in the treatment of AS due to the limited number of treatment options available, especially regarding the limited mechanisms of action and mode of administration.

Current guidelines recommend offering AS patients who fail to achieve an adequate response with a first biologic therapy the option to switch to a second biologic, either a TNFi or IL-17A inhibitor.[2,6,29] Currently, clinicians can only choose to switch from a TNFi to an IL-17A inhibitor or *vice versa*, or switch to an alternative treatment with the same mechanism of action, Ultimately, with only two mechanisms currently available, there are very limited treatment options for AS patients.

A recent cohort study of patients with axSpA demonstrated that on average, response to a second TNFi was worse than response to a first TNFi, especially in patients who never responded to their first TNFi.[31] Therefore, patients with axSpA require treatments with different mechanisms of action to enable greater treatment choices for patients who respond

inadequately to current treatment options. This is especially relevant for patients who cannot tolerate the adverse effects associated with TNFi and cannot be treated with TNFi at all.[13]

Extra-articular manifestations are common in patients with AS, and the presence of which can further limit the treatment options available. Uveitis, psoriasis and IBD are common extra-articular manifestations, with a prevalence of 25.8%, 9.3% and 6.8%, respectively.[32] However, secukinumab and ixekizumab are not recommended in patients with IBD, in-line with their SmPC, as cases of new or exacerbated IBD have been reported in treated patients.[5,33] AbbVie are currently investigating the use of upadacitinib in patients with IBD, although no link between upadacitinib and worsening IBD has currently been identified, and there are no contra-indications for patients with IBD receiving upadacitinib for other licensed indications.[1] Therefore, patients with IBD are currently limited to one mechanism of action (TNFi) when considering their treatment options, but could benefit significantly by the introduction of another mode of action not contra-indicated for the particular EAM.

When patients with axSpA, including those with AS, were specifically asked about their preferences regarding treatment administration, 90% chose to receive their medication at home and 78.6% preferred a treatment they could administer themselves.[34] Similarly, 51.4% of axSpA patients in this study would prefer an oral treatment, stating that the main advantages were the easy administration (58.3%), no need for a special skill (33.3%) and no requirement for refrigeration (16.7%).[34] This demonstrates a clear patient desire for a more convenient oral treatment option in AS, where patients have greater autonomy over their own care and can adapt their treatment around their current lifestyles. This is especially important to patients with AS, as most AS patients are diagnosed before the age of 45,[19,20] and so are at a crucial age of educational, professional and social development. Similarly, AS patients with needle-phobia would benefit from an oral therapeutic option to save them from the distress caused by current injectable treatments.

The main resource uses associated with current comparators, which are all administered via subcutaneous injection or intravenous infusion, are treatment, administration and monitoring. As an oral therapy, upadacitinib would avoid the cost and resource use associated with subcutaneous or intravenous comparators, such as the initial training for self-injection.

The recent COVID-19 pandemic recently demonstrated the need for more oral therapeutic options due to their reduced requirements for monitoring, injection training and nurse visits compared to current injectable therapies, which allows more patients to be seen remotely, aligning with NHS guidance.[35] Additionally British Society of Rheumatology (BSR) guidance

during the COVID-19 pandemic recommended initiating patients on treatments with shorter half-lives, especially highlighting JAK inhibitors.[36] [36]

Patients with AS experience reduced health-related QoL, across both physical and mental domains and do not achieve substantial improvements in QoL with current treatments. In a 2015 retrospective chart review (n=129) assessing the effect of TNFi treatment on pain, fatigue and QoL, after at least 10 weeks of TNFi therapy, 60% of patients had clinically significant improvements (>30%) in pain and QoL factors. However, out of these patients, only 22% had significant relief of both pain and fatigue. Hence, current treatments may improve several aspects of patients' symptoms, but do not improve overall patient QoL substantially, and fail to significantly reduce the disease burden of AS.[37]

Additionally, QoL in patients with AS is further reduced when patients are irresponsive or intolerant to a specific treatment, a common occurrence in AS management. For example, a large multinational real-world sample in Europe and the USA (n=1,889) assessed the effect of failure to respond or tolerate biologic therapy in AS patients.[38] AS patients who were non-responsive or intolerant to biologic treatment had significantly worse (lower) scores for EQ-5D (0.55 vs 0.82) and SF-36: physical component summary (45.9 vs 73.3), mental component summary (57.5 vs 69.6) and social function scale (53.8 vs 75.2) than those not failing (all $p<0.0001$).[38]

B.1.4 Equality considerations

It is not considered that this appraisal will exclude any people protected by equality legislation; or lead to a recommendation that would have a different impact on people protected by equality legislations than on the wider population; or lead to recommendations that would have an adverse impact on people with a particular disability.

However, all current treatments for active AS patients who have failed conventional therapy are administered via subcutaneous injection or intravenous infusion. Patients with needle phobia are significantly disadvantaged. As upadacitinib is the first oral therapy available for these patients, any recommendation made by the committee would support positive access to a treatment option for patients with needle phobia.

B.2. Key drivers of the cost effectiveness of the comparators

B.2.1 Clinical outcomes and measures

A total of five NICE technology appraisals (TA) describing treatments for AS and/or AxSpA were identified:

- TA383: TNFi for AS and nr-axSpA (replacing TA233 and TA143)
- TA407: Secukinumab for active AS after treatment with NSAIDs or TNFi
- TA497: Golimumab for treating nr-axSpA
- TA718: Ixekizumab for treating axSpA
- TA719: Secukinumab for treating nr-axSpA

TA383 was a multiple technology appraisal (MTA), whilst the remaining TAs were single technology appraisals (STA). All submissions presented cost-effectiveness analyses as their main form of economic evidence, with the exception of TA497, which opted for a fast-track appraisal (FTA) utilising a cost comparison analysis.

The most common measures of clinical effectiveness used in each of the submissions were assessment of ankylosing spondylitis 20 (ASAS20), ASAS40, BASDAI50, BASDAI change from baseline (CFB) and Bath ankylosing spondylitis functional index (BASFI) CFB, all of which are measures of response, physical function or disease activity associated with AS. Each of the efficacy measures is further described in Table 3. Typically, ASAS20 and ASAS40 were reported as 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 the most relevant to long-term clinical outcomes for patients and have been specified in the scope for previous NICE appraisals in this disease setting, as outlined in Table 4. Across all identified TAs and all common measures of clinical effectiveness, there was little evidence to suggest any one treatment offered statistically significant improvements in outcomes over other treatments. The discussion around comparable efficacy is a common theme and conclusion amongst all identified TAs. An overview of key clinical outcomes used in each of the TAs and their use in economic evaluations is presented in **Error! Reference source not found.**.

Beyond these key clinical outcomes, discontinuation has also been discussed during committee review. Across all TAs described above, observed unadjusted discontinuation rates informed by the pivotal trial appear to be numerically consistent across treatments. However, none of the appraisals included discontinuation as an outcome of evaluation in their approach to evidence synthesis and 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. The exceptions to this were TA407, which assumed rates derived directly from pivotal trial data, and TA497, which did not include discontinuation in its cost-comparison analysis. Across all appraisals, approaches to discontinuation were not strongly criticised by review groups, however, with the exception of TA497, all review groups preferred the assumption of equal rates of discontinuation across treatments.

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 40	Improvement of ≥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.		

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
TA383[2] TNFα inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis	Certolizumab pegol; golimumab; adalimumab; etanercept; infliximab; 'conventional therapy'	Companies: CEA; ERG: CEA	ASAS20	Yes, for all TNFα inhibitors – versus placebo; the meta-analysis showed no statistically significant differences between the 5 TNFα inhibitors for efficacy outcomes at 10–16 weeks.	Yes	The Committee concluded that TNFα inhibitors were clinically effective compared with placebo and, given the lack of difference in effect between them, they should be considered as a class with broadly similar, even if not completely identical, effects.
			ASAS40		Yes	
			BASDAI50		Yes	
			BASDAI CFB		Yes	
			BASFI CFB		Yes	
			MASES		No	
TA407[6] Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNFα inhibitors	Secukinumab; etanercept; certolizumab pegol; adalimumab; golimumab; infliximab	Company: CEA; ERG: CEA	ASAS20	No (A)	No	The company's mixed-treatment comparison showed higher efficacy for secukinumab 150 mg compared with placebo across all outcomes for the whole population and also for the biologic-naive subgroup. The committee concluded that secukinumab has a similar efficacy to the TNFα inhibitors.
			ASAS40	No (A)	No	
			BASDAI50	No (A)	Yes	
			BASDAI CFB	Yes – but only infliximab was predicted to be significantly superior to all other treatments (A)	Yes	
			BASFI CFB	No (A)	Yes	
TA497[39] Golimumab for treating non-	Golimumab; adalimumab; certolizumab	Company: CCA	ASAS20	No	No	The clinical effectiveness of golimumab was similar to adalimumab, etanercept and
			ASAS40	No	No	
			BASDAI50	No	No	

radiographic axial spondyloarthritis	pegol; etanercept		BASDAI CFB	Yes – but golimumab significantly superior to etanercept only	No	certolizumab pegol for BASFI, BASDAI and BASMI scores. Golimumab was statistically significantly superior to etanercept and adalimumab for change from baseline in BASFI score, etanercept for change from baseline in BASDAI score, and adalimumab for change from baseline in BASMI score. The committee concluded that the clinical effectiveness of golimumab was likely to be similar to those of the comparators.
			BASFI CFB	Yes – but golimumab significantly superior to adalimumab and etanercept only	No	
			BASMI CFB	Yes – but golimumab significantly superior to adalimumab only	No	
TA718[7] 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[40] 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
			ASAS 40	No (B)	No	
			BASDAI 50	No (B)	Yes	
			BASDAI CFB	No (B)	Yes	
			BASFI CFB	No (B)	Yes	

						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 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 **Error! Reference source not found.** include:

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

Across STA appraisals, there was consensus that these were the standard resources required to inform an economic submission. By contrast, TA497[39] (the only other appraisal for AS conducted by the FTA process) and all other appraisals assessed under the FTA process have solely focused 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.

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 (see Section **Error! Reference source not found.**). However, consistent with TA497[39], the main resource use component associated with each treatment is the underlying drug cost. 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, TA407, TA497, TA718 and TA719),[2,6,7,39,40] drug acquisition costs for all treatments were sourced from the British National Formulary (BNF),[41] with relevant patient access schemes (PAS) assessed. All treatments are assumed to be administered at licensed dose, based on the doses cited by the BNF,[41] relevant SmPCs[1,33,42] and those administered in pivotal studies,[43,44] ensuring that costs represent clinically feasible doses (see Section B.4.2.2).

Similarly, drug administration cost (i.e., those for subcutaneous injections for secukinumab and ixekizumab) and monitoring cost components were identified from previous NICE technology appraisals (TA383, TA407, TA497, TA718 and TA719),[2,6,7,39,40] and are applied consistently with these previous approaches (Section **Error! Reference source not found.**). Cost data was sourced from NHS Reference Costs 2019/20,[45] previous NICE technology appraisals[2,6,7,46,47] and the PSSRU.[48]

B.3. Clinical effectiveness

B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken to identify all the relevant clinical effectiveness evidence (efficacy and safety) of interventions for the treatment of AS. Full details of the process and methods to identify and select the relevant clinical evidence are summarised in Appendix C.

The SLR identified 191 records for inclusion, of which, 152 records detailed interventions anticipated to be applicable to the scope. A total of 103 full reports and 49 conference abstracts were included across 10 difference interventions. Record reporting data on biosimilars were identified for adalimumab (HS016,[49] Exemptia,[50] BAT1406,[51] and IBI303[52]), etanercept (rhTNFR:Fc[53] and Yisaipu[54]), and infliximab (CT-P13[55] and BCD-055[56]), as presented in Table 5.

Table 5. Studies identified during the clinical SLR

Intervention	Full reports	Conference abstracts	Total
Adalimumab	15	0	15
Certolizumab	4	5	9
Etanercept	29	0	29
Golimumab	13	7	20
Infliximab	15	0	15
Secukinumab	18	27	45
Upadacitinib	1	6	7
Adalimumab biosimilars	3	3	6
Etanercept biosimilars	2	0	2
Infliximab biosimilars	3	1	4
Total	**103**	**49**	**152***

No studies were identified that directly compared upadacitinib to any of the active biologic comparators.

It should also be noted an updated search was conducted on 28 October 2021 to identify any relevant articles which may have been published following the initial search in March 2021. This approach was agreed with NICE in light of delays related to NICE confirming a submission date for the appraisal and provides a pragmatic solution in terms of running searches within 6 months of submission. After removal of duplicates, 426 potentially relevant articles were identified. These were independently screened by two reviewers for eligibility. Of these, 369 were excluded at the title and abstract screening stage, the remaining 57 articles were retrieved for full text screening. In total six articles met the eligibility criteria. However, these studies met criteria for inclusion in the SLR which was conducted from a global perspective and were either not relevant to the decision problem specified in this appraisal, or did not provide data which would impact on the NMA (Appendix C).

B.3.2 List of relevant clinical effectiveness evidence

Evidence to support the effectiveness of upadacitinib for the treatment of active ankylosing spondylitis is derived from the SELECT-AXIS1 and SELECT-AXIS2 trials.

SELECT-AXIS1 was a Phase II/III RCT evaluating the safety and efficacy of upadacitinib at 14 weeks (period 1), with a 104 week long-term extension (period 2) (Figure 2). Period 1 enrolled 187 patients who received with 15 mg QD of upadacitinib or placebo. During period 2, all patients received 15 mg QD upadacitinib for 90 weeks. The primary endpoint was ASAS40 response at week 14.

SELECT-AXIS2 is an ongoing Phase III RCT evaluating the safety and efficacy of upadacitinib in patients with active axial spondylitis, including biologic disease-modifying antirheumatic drug inadequate responder (bDMARD-IR) AS (study 1) and non-radiographic axial spondylitis (nr-axSpA) (study 2) (**Figure 5**). SELECT-AXIS2 Study 1 enrolled 386 bDMARD-IR patients with active AS who received with 15 mg QD of upadacitinib or placebo. The primary endpoint was the same as used for SELECT-AXIS1, ASAS40 response at week 14. Please note that only patients with active AS from Study 1 of SELECT-AXIS2 will be reported in this submission.

A summary of SELECT-AXIS1 and SELECT-AXIS2 is provided in Table 6 and Table 7, respectively.

Table 6. Clinical effectiveness evidence – SELECT-AXIS1

Study	**SELECT-AXIS1 (NCT03178487)** **van der Heijde et al (2019)**		
Study design	Phase 2/3, multicentre, randomised, double-blind, placebo-controlled trial		
Population	Adults with active AS (BASDAI ≥4 and patient's assessment of back pain ≥4), who fulfilled modified New York criteria, were previously untreated with bDMARDs and had inadequate response to at least two or intolerance or contraindication to NSAIDs.		
Intervention(s)	Upadacitinib 15 mg		
Comparator(s)	Placebo		
Indicate if trial supports application for marketing authorisation	Yes	Indicate if trial used in the economic model	Yes
Rationale for use/non-use in the model	Relevant population/outcomes reported		
Primary outcome	• ASAS40		
Secondary outcomes	• ASDAS CFB • SPARCC score (spine) • BASDAI50 • ASQoL CFB • ASAS PR • BASFI CFB • BASMI CFB • MASES CFB • WPAI • ASAS HI CFB • Adverse events		
All other reported outcomes	• Total back pain • MRI SPARCC		

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; mSASSS: modified stoke ankylosing spondylitis spinal score; NSAIDs: non-steroidal anti-inflammatory drugs; SPARCC: Spondyloarthritis Research Consortium of Canada; WPAI: work productivity and activity impairment;

Source: SELECT-AXIS1 protocol,[57] SELECT-AXIS1 CSR,[58] van der Heijde et al (2019)[44]

Table 7. Clinical effectiveness evidence – SELECT-AXIS2

Study	SELECT-AXIS2 Study 1 (NCT 04169373)		
Study design	Phase 3, multicentre, randomised, double-blind, placebo-controlled trial		
Population	Adults with active AS (BASDAI ≥4 and patient's assessment of back pain ≥4), who fulfilled modified New York criteria, previously treated with 1 or 2 bDMARDs (TNFi or IL-17A inhibitors), which they discontinued due to lack of efficacy or intolerance.		
Intervention(s)	Upadacitinib 15 mg		
Comparator(s)	Placebo		
Indicate if trial supports application for marketing authorisation	Yes	Indicate if trial used in the economic model	Yes
Rationale for use/non-use in the model	Relevant population/outcomes reported		
Primary outcome	• ASAS40		
Secondary outcomes	• ASDAS CFB • CFB in MRI SPARCC score (spine) • BASDAI50 • Proportion of patients with ASDAS inactive disease (ASDAS score < 1.3) • Proportion of patients with ASDAS low disease activity (ASDAS score <2.1) • CFB in patient's assessment of total back pain • CFB in patient's assessment of nocturnal back pain • ASQoL CFB • ASAS PR • BASFI CFB • BASMI CFB • MASES CFB • ASAS HI CFB • Adverse events		
All other reported outcomes	• MRI SPARCC		

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; mSASSS: modified stoke ankylosing spondylitis spinal score; NSAIDs: non-steroidal anti-inflammatory drugs; SPARCC: Spondyloarthritis Research Consortium of Canada; WPAI: work productivity and activity impairment;

Source: SELECT-AXIS2 protocol,[59]

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

The methodology of relevant studies is summarised in Section B.3.6.

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

The statistical methods and definition of study groups for the relevant studies are summarised in Section B.3.6.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from two large phase 2/3 trials conducted in line with the requirements of the regulatory bodies. The complete quality assessment of SELECT-AXIS1 and SELECT-AXIS2 is provided in Table 8. The quality assessment of the trials identified during the clinical SLR and used to inform the indirect treatment comparison (ITC) is provided in Appendix C.

Table 8. Quality assessment results for SELECT-AXIS1 and SELECT-AXIS2

	SELECT-AXIS1 (NCT03178487)	SELECT-AXIS2 (NCT04169373)
Was randomisation carried out appropriately?	Yes, all eligible patients were randomised in a 1:1 ratio using interactive response technology that assigned a unique identification number according to a randomisation schedule generated by the statistics department of the sponsor. Randomisation was stratified by screening concentrations of high-sensitivity C-reactive protein and geographical region (USA and Canada, Japan, rest of the world).	Yes, all eligible patients were randomised in a 1:1 ratio using interactive response technology that assigned a unique identification number according to a randomisation schedule generated by the statistics department of the sponsor. Randomisation was stratified by screening concentrations of high-sensitivity C-reactive protein and geographical region (USA and Canada, Japan, rest of the world).
Was the concealment of treatment allocation adequate?	Yes, all study personnel, including the sponsor, investigator, and study site personnel, and the patient were blinded to the treatment allocation. To maintain the concealment, upadacitinib and placebo were presented as orally administered tablets that were identical in appearance.	Yes, all study personnel, including the sponsor, investigator, and study site personnel, and the patient were blinded to the treatment allocation. To maintain the concealment, upadacitinib and placebo were presented as orally administered tablets that were identical in appearance.
Were the groups similar at the onset of the study in terms of prognostic factors?	Yes, the baseline characteristics of the two treatment arms were generally balanced, see Table 13	Yes, the baseline characteristics of the two treatment arms were generally balanced, see Table 20
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, all study personnel, including the sponsor, investigator, and study site personnel, and the patient were blinded to the treatment allocation	Yes, all study personnel, including the sponsor, investigator, and study site personnel, and the patient were blinded to the treatment allocation
Were there any unexpected imbalances in drop-outs between groups?	No, a similar number of patients discontinued in both study arms, 5 in the upadacitinib arm and 4 in the placebo arm.	No, a similar number of patients discontinued in both study arms, 5 in the upadacitinib arm and 6 in the placebo arm.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, all measured outcomes have been reported.	No, all measured outcomes have been 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, the analysis did not include intention-to-treat analysis. Missing data was accounted for using non-responder imputation.	No, the analysis did not include intention-to-treat analysis. Missing data was accounted for using non-responder imputation in conjunction with multiple imputation (NRI-MI).
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[60]		

B.3.6 Clinical effectiveness results of the relevant trials

SELECT-AXIS1 and SELECT AXIS2 were high-quality trials where the inclusion criteria selected patients with active AS, defined as a BASDAI ≥ 4 and a Patient's Assessment of Total Back Pain ≥ 4 based on a 0-10 NRS at the screening and baseline visits.[44,57] This corresponds to the definition of active AS applied in current BSR guidance in the UK.[61] Therefore, the patients enrolled in both trials are considered generalisable to the UK population of patients with active AS. Similarly, other measurements for disease activity, functional impairment and radiographic severity (Table 13 and Table 20), were thought to be generalisable between the SELECT-AXIS1 and SELECT-AXIS2 trial populations and the UK population of patients with active AS,[62,63] when discussed by a panel of clinical experts during an advisory board held by AbbVie.[4]

B.3.6.1 SELECT-AXIS1

Key points from SELECT-AXIS1

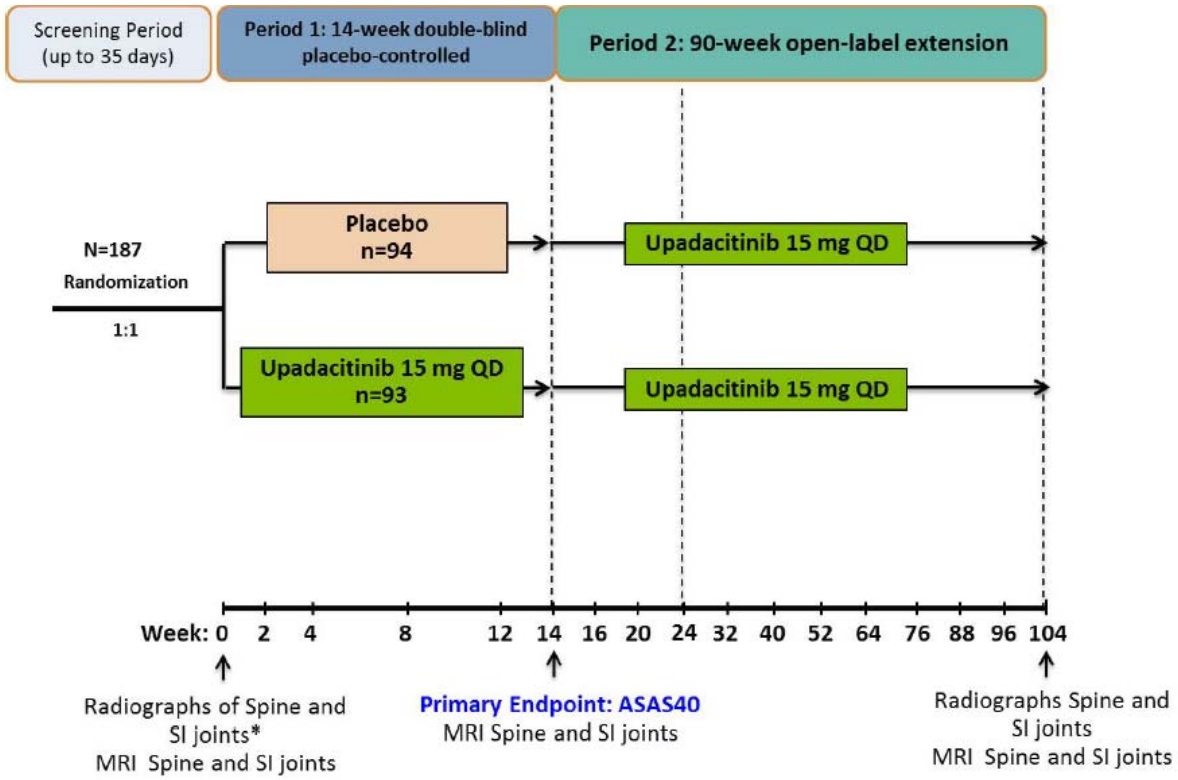
- Significantly more patients achieved ASAS40 treatment response in the upadacitinib arm compared to the placebo arm at week 14 (52% vs 26%).
- A significant improvement was also seen in the upadacitinib arm compared to the placebo arm at week 14 for disease activity (ASAS partial remission, BASDAI50, ASDAS), function (BASFI) and MRI outcomes (SPARCC MRI spine).
- The proportion of patients achieving BASDAI50 in the upadacitinib arm was significantly higher than those in the placebo arm, 45.2 (35.0, 55.3) and 23.4 (14.8,32.0), respectively.
- The rate of adverse events was similar between the two treatment groups (62% in the upadacitinib arm versus 55% in the placebo arm) at week 14, and no serious infections, herpes zoster, malignancy, venous thromboembolic events or deaths were reported. One serious adverse event was reported in each arm.
- Results from SELECT-AXIS1 support the option for patients with active AS to be treated with upadacitinib

B.3.6.1.1 Study design

SELECT-AXIS1 is a phase 2/3 multicentre, randomised, double-blind, placebo-controlled, two-period, parallel-group study whose primary objective was to demonstrate the safety and efficacy of upadacitinib in AS.

Patients were randomised (1:1) to receive oral upadacitinib 15 mg once daily or oral placebo for 14 weeks (Period 1). Patients who completed Period 1 entered Period 2: an open-label extension to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD over 90 weeks. The study design of SELECT-AXIS1 is described in Figure 2. A summary of the methodology for SELECT-AXIS1 is provided in Table 9. The sections that follow give additional information on eligibility criteria (Section B.3.6.1.3) and statistical methods (Section B.3.6.1.4).

Figure 2. Study design of SELECT-AXIS1



* Radiographs conducted during the screening period

ASAS40: assessment of SpondyloArthritis international society 40 response; MRI: magnetic resonance imaging; QD: once daily; SI: sacroiliac;
Source: van der Heijde et al. (2019)[44]

Table 9. Summary of trial methodology - SELECT-AXIS1

Trial name	SELECT-AXIS1 (NCT03178487)
Location	North America, Australia and New Zealand, Europe, Asia,
Trial design	Phase 2/3 multicentre, randomised, double-blind, placebo-controlled, two-period, parallel-group
Eligibility criteria for participants	Adults with active AS, who fulfilled modified New York criteria, were previously untreated with bDMARDs and had inadequate response to at least two or intolerance or contraindication to NSAIDs. Additional details are provided in Table 10.
Settings and locations where data were collected	The study was conducted in 62 academic centres and hospitals in 20 countries across North America, Australia and New Zealand, Europe and Asia. This included 5 UK centres.
Study drugs	Upadacitinib 15 mg QD Oral placebo
Concomitant medications	Patients could continue their stable background csDMARD therapy, restricted to MTX, SSZ, hydroxychloroquine and leflunomide, throughout the study. A combination of up to two background csDMARDs was allowed except for the combination of MTX and leflunomide. The following concomitant medications or therapies were not permitted at any time during the study: • Any JAK inhibitor • Corticosteroids • Biologic therapies • Strong CYP3A inhibitors or inducers • Opiates and marijuana • Investigational drugs • Traditional Chinese medicine
Primary outcome	The proportion of patients with ASAS 40 response at Week 14, defined as a ≥ 40% improvement and an absolute improvement of ≥ 2 units (on a scale of 0 to 10) from baseline in at least three of the following four domains, with no worsening in the remaining domain: • Patient's Global Assessment – represented by the PtGA NRS score (0 to 10); • Pain – represented by the Patient's Assessment of Total Back Pain NRS score (0 to 10); • Function – represented by the BASFI NRS score (0 to 10); • Inflammation – represented by the mean of the two morning stiffness-related BASDAI NRS scores (mean of items 5 and 6 of the BASDAI [0 to 10]).
Other outcomes used in the economic model/specified in the scope	Disease activity: • Change from baseline in ASDAS • Proportion of patients with BASDAI 50 response (defined as 50% improvement in the BASDAI) • Proportion of patients with ASAS partial remission (PR) (defined as an absolute score of ≤ 2 units for each of the four domains identified in ASAS 40) • Change from baseline in ASAS HI

Trial name	SELECT-AXIS1 (NCT03178487)
	• ASAS 5/6 (20% improvement from baseline in five out of the following six domains: BASFI, patient's assessment of total back pain, PtGA, inflammation [mean of items 5 and 6 of the BASDAI] lateral lumbar flexion from $BASMI_{lin}$, and high sensitivity CRP [hsCRP]) • ASDAS Inactive Disease (ASDAS score < 1.3) • ASDAS Major Improvement (change from baseline at least 2.0) • ASDAS Clinically Important Improvement (change from baseline of at least 1.1) • Change from baseline in BASDAI Functional capacity: • Change from baseline in BASFI • Change from baseline in $BASMI_{lin}$ 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 Peripheral symptoms: • Change from baseline in MASES Adverse events HRQoL: • Change from baseline in AS QoL • Change from baseline in WPAI
Pre-planned subgroups	Pre-specified subgroup analyses based on baseline disease characteristics and stratification factors was conducted.
AS: ankylosing spondylitis; 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; FACIT-F: Functional assessment of chronic illness therapy - fatigue; HI: health index; ISI: insomnia severity 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; SJC: swollen joint count; SPARCC: spondyloarthritis research consortium of Canada; SSZ: sulfasalazine; TJC: tender joint count; UK: United Kingdom; WPAI: work productivity and activity impairment; Source: SELECT-AXIS1 protocol[57]	

B.3.6.1.2 Study treatments

Two groups of patients were randomised 1:1 to receive either upadacitinib 15 mg QD or oral placebo for 14 weeks (Period 1) (Figure 2). At week 14, all patients either continued or switched to upadacitinib 15 mg QD for a further 90 weeks (Period 2).

B.3.6.1.3 Eligibility criteria

Key eligibility criteria for patients in SELECT-AXIS1 are provided in Table 10.

Table 10. Key inclusion and exclusion criteria for SELECT-AXIS1

Key inclusion criteria	Key exclusion criteria
• Male or female ≥ 18 years of age. • Patients with a clinical diagnosis of AS and meeting the modified New York Criteria for AS. • Patients must have baseline disease activity as defined by having a BASDAI score ≥ 4 and a Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 – 10 NRS at the Screening and Baseline Visits. • Patients have had an inadequate response to at least two NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses, or patient has an intolerance to or contraindication for NSAIDs as defined by the Investigator. For further details, see the study protocol[57]	• Prior exposure to any JAK inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib). • Prior exposure to any biologic therapy with a potential therapeutic impact on axSpA • Patient has been treated with any investigational drug within 30 days or • five half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study. • Intra-articular joint injections, spinal/paraspinal injection(s), or parenteral administration of corticosteroids within 28 days prior to the Baseline Visit. Inhaled or topical corticosteroids are allowed. • Patient on any other DMARDs (other than those allowed), thalidomide, or • apremilast within 28 days or five half-lives (whichever is longer) of the drug prior to the Baseline Visit. • Patient on opioid analgesics (except for combination acetaminophen/codeine or acetaminophen/hydrocodone which are allowed) or use of inhaled marijuana within 14 days prior to the Baseline Visit. • Patient has a history of inflammatory arthritis of different aetiology other than axSpA (including but not limited to RA, PsA, mixed connective tissue disease, systemic lupus erythematosus, reactive arthritis, scleroderma, polymyositis, dermatomyositis, fibromyalgia), or any arthritis with onset prior to 17 years of age. • Patient with extra-articular manifestations (e.g., psoriasis, uveitis, or IBD) that are not clinically stable for at least 30 days prior to study entry. • Patient has total spinal ankylosis. • Patient has undergone spinal or joint surgery at joints to be assessed within this study within 60 days prior to the Baseline Visit or patient has been diagnosed with a spinal condition that may interfere with study assessments (i.e., disc herniation, degenerative spine

	disease, etc.) in the opinion of the Investigator. • Patient is permanently wheelchair-bound or bedridden. For further details, see the study protocol[57]
ANC: absolute neutrophil count; ALT: Alanine transaminase; AS: ankylosing spondylitis; AST: aspartate transaminase; axSpA: axial spondyloarthritis; BASDAI: Bath ankylosing spondylitis disease activity index; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; CXR: chest radiography; CYP: cytochrome; DMARDs: disease modifying antirheumatic drugs; ECG: echo cardiogram; GFR: glomerular filtration rate; IBD: irritable bowel disease; IEC: independent ethics committee; IRB: institutional review board; JAK: Janus kinase; MDRD: modification of diet in renal disease; MRI: magnetic resonance imaging; MTX: methotrexate; NMSC: non-melanoma skin cancer; NRS: numerical rating scale; NSAIDs: non-steroidal anti-inflammatory drugs; PSA: psoriasis; RA: rheumatoid arthritis; SSZ: sulfasalazine; TB: tuberculosis; ULN: upper limit of normal; WBC: white blood cell; Source: SELECT-AXIS1 protocol[57]	

B.3.6.1.4 Statistical analysis and definition of study groups

A summary of the statistical analysis of SELECT-AXIS1 is provided in Table 11.

Table 11. Statistical analysis and definition of study groups in SELECT-AXIS1

	SELECT-AXIS1 (NCT03178487)
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 meet any major protocol deviations up to Week 14 in Period 1 of the study. Additional analysis of the primary efficacy endpoint was conducted on the Per Protocol analysis set, to evaluate the impact of major protocol deviations. 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 "as treated" treatment group, regardless of the treatment randomised. The "as treated" was determined by the treatment the patient received during the majority of the patient's drug exposure time in the analysis period.
Statistical analysis of primary endpoints	The primary efficacy endpoint for regulatory purposes is ASAS 40 response at Week 14. The primary estimated was the difference in the proportion of AS patients who achieved ASAS 40 response at Week 14 and did not discontinue study drug by Week 14, comparing those who are randomised to the upadacitinib group and received study drug to those who are randomised to placebo and received study drug. The primary analysis was conducted on the FAS based on randomised treatment groups. Point estimate and 95% CI using normal approximation were provided for the response rate for each randomised treatment group. Comparisons of the primary endpoint were made between upadacitinib and the placebo group using the Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor of hsCRP level (≤ ULN vs. > ULN). Point estimate, 95% CI using normal approximation and p-value for the treatment comparison were

	presented. The nominal p-value constructed using the CMH test was provided. The multiplicity adjusted testing results (significant or not significant) were also provided. For the primary estimate, NRI data handling was used. To facilitate the interpretation of the estimate, the number and percentage of non-responders for ASAS40 were summarised into three categories: 1. Patients who discontinue study drug by Week 14 2. Patients who did not discontinue study drug but missing Week 14 ASAS 40 measurements 3. Patients with ASAS 40 measurements observed and on study drug at Week 14 but did not meet ASAS 40 response criteria
Statistical analysis of secondary endpoints	For binary endpoints, frequencies and percentages were reported for each randomised treatment group. The primary estimate was the same as that for the primary efficacy endpoint, except for the definition of the efficacy measurement. NRI data handling was used to analyse the primary estimate. Supplementary analysis using AO data handling was also conducted. To explore various missing data assumptions including MNAR, tipping point analysis will also be conducted for ASAS 20 at Week 14. Point estimate and 95% CI using normal approximation was provided for the response rate for each randomised treatment group. Treatment comparisons were made between upadacitinib and the placebo group using the Cochran-Mantel-Haenszel. The CMH test adjusts for the main stratification factor of hsCRP level (≤ ULN vs > ULN). Point estimate, 95% CI using normal approximation and the p-value for the treatment difference will be presented. For continuous key secondary efficacy endpoints, the estimate is the difference in mean change from baseline at Week 14 under the assumption that patients with missing data including those due to premature discontinuation of study drug can have their measurements at Week 14 predicted by their observed data and the observed data for other patients for their respective assessments during follow-up. The comparison was upadacitinib vs placebo for patients randomised and treated with at least one dose of study drug. For the primary estimate of the continuous key secondary efficacy endpoints, statistical inference was conducted using the MMRM model and the associated data handling with the main stratification factor of hsCRP level (≤ ULN vs > ULN). The LS mean and 95% CI were reported for each randomised treatment group; the LS mean treatment difference and associated 95% CI and p-value were reported comparing upadacitinib with the placebo group. The supplementary analysis for secondary continuous variables was conducted on AO cases using the ANCOVA model with treatment and the stratification factor of hsCRP (≤ ULN vs > ULN) as the fixed factor and the corresponding baseline value as the covariate. The corresponding estimate was the difference in the mean change from baseline in the efficacy endpoints at Week 14 regardless of premature discontinuation of study drug. To explore various missing data

	assumptions including MNAR, the tipping point analysis will also be conducted using MI as additional supplementary analysis. To account for any multiplicity issues that may arise when comparing multiple endpoints, the Hochberg procedure, a multiplicity adjustment method, was applied to analyse the secondary trial endpoints. The multiplicity-controlled endpoints were tested in a sequential manner with an initially assigned α of 0.05. Significance could be claimed for a lower ranked endpoint only if the previous endpoint in the sequence met the requirements of significance. ASAS HI could be evaluated only if the group of endpoints tested by Hochberg procedure were all statistically significant. As per the Hochberg procedure, all endpoints were tested using the assigned α according to the magnitude of nominal P-value starting from the largest one. If an endpoint was significant, all endpoints with smaller P-values were significant. If an endpoint was not significant, then the procedure advanced to the next endpoint.
Statistical analysis of safety endpoints	Safety analysis was carried out using the safety analysis set. Standard safety analysis by the "as treated" treatment group of upadacitinib and placebo groups will be performed on safety data in period 1. No protocol-defined treatment switching will occur prior to these time points. Missing safety data was not imputed.
Sample size and power calculation	The planned sample size of 170 will provide at least 90% power to detect a 26% difference in ASAS40 response rates at week 14 (assuming a placebo ASAS40 response rate of 20%), at two-sided α=0.05 and accounting for 10% dropout rate.
Handling of missing data and participant withdrawals	Non-responder imputation (NRI): the NRI approach handled data for the primary estimate for binary variables. Patients who prematurely discontinue from study drug were considered as non-responders for all subsequent visits after discontinuation. In addition, any patient with any missing value for binary variables at a specific visit were treated as non-responders for that visit. As observed (AO): The as observed data handling did not impute values for missing evaluations and so a patient who did not have an evaluation at a scheduled visit was excluded from the AO analysis for that visit. Regardless of premature discontinuation of study drug, all observed data was used in the analysis. The AO data handling was used to facilitate the supplementary analysis for both binary and continuous variables. Mixed effect model repeat measurement (MMRM): The repeated measure analysis was conducted using mixed model including observed data at all visits. For the MMRM analysis, data collected after premature discontinuation of study drug was excluded. The mixed model includes the categorial fixed effects of treatment, visit and treatment-by-visit interaction, main stratification factors at randomisation and the continuous fixed covariates of baseline measurement. An unstructured variance covariance matrix was used. The parameter estimation was based on the assumption of data being missing at random and using the method of restricted maximum likelihood (REML). MMRM was used for the primary estimated of continuous variables.
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-AXIS1 statistical analysis plan[64]	

B.3.6.1.5 Patient disposition and baseline characteristics

Participant disposition

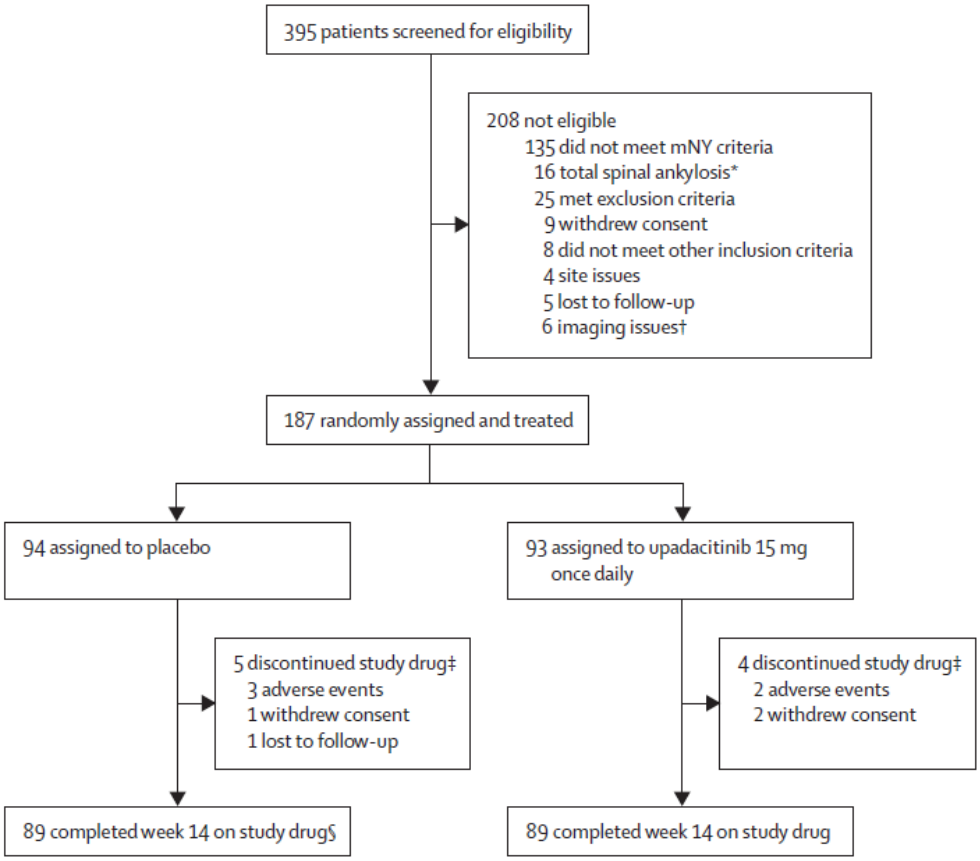
A total of 187 patients were randomised in Period 1 and were treated with either upadacitinib (n=93) or placebo (n=94). A summary of patient disposition is provided in Table 12 and Figure 3.

The proportion of patients who discontinued was low and comparable between the two study arms (upadacitinib: 4 [4.3%]; placebo: 5 [5.3%]). For patients in the upadacitinib group, the reasons for discontinuation were adverse events (2 [2.2%]) and patient withdrawal (2 [2.2%]). For patients in the placebo group, the reasons for discontinuation were adverse events (3 [3.2%]), patient withdrawal (1 [1.1]), lost to follow-up (1 [1%]) and other(1 [1%]).

Table 12. Patient disposition in SELECT-AXIS1

	Placebo (N=94) n (%)	**Upadacitinib 15 mg QD (N=93) n (%)**
Patient status		
Randomised	94 (100)	93 (100)
Completed	89 (94.7)	89 (95.7)
Discontinuations	5 (5.3)	4 (4.3)
Reasons for discontinuations		
Adverse events	3 (3.2)	2 (2.2)
Withdrew consent	1 (1.1)	2 (2.2)
Lost to follow-up	1 (1.1)	0
QD: once per day; Source: van der Heijde et al. (2019)[44]		

Figure 3. Patient disposition in SELECT-AXIS1



* Total spinal ankylosis was defined as bridging syndesmophytes (fusion) in a total sum of five or more segments of the C2-T1 or T12-S1 spine (e.g., a case with two segments fused in the cervical and three segments fused in the lumbar spine would be considered positive for total spinal ankylosis).

†Imaging issues included technical issues at imaging facility, delay in imaging transfer to central reading, and scheduling issues.

‡Primary reason for discontinuation given.

§One patient discontinued study drug but completed period 1 visits.

A patient could have more than one reason for screening failure.

mNY=modified New York.

Source: van der Heijde (2019)[44]

Baseline characteristics

Demographic characteristics were broadly similar between the two treatment groups. The mean age was similar in both groups (placebo: 43.7 [SD: 12.1]; upadacitinib: 47.0 [SD: 12.8]). The majority of patients were male (placebo: 73%; upadacitinib: 68%) and the majority were of white race (placebo: 81%; upadacitinib: 85%). Medium BMI was 27 in both treatment groups. Disease duration since diagnosis and the time from appearance of symptoms was similar in both treatment arms, (6.0 and 7.8 years since diagnosis and 14.0 and 14.8 years since the appearance of symptoms, in the placebo and upadacitinib treatment arms,

respectively). This difference in the duration between the onset of symptoms and diagnosis is due to an average diagnostic delay of 8.57 years observed in patients with AS.[16,17] Baseline characteristics are summarised in Table 13.

Table 13. Baseline characteristics of patients in SELECT-AXIS1

	Placebo (N=94) n (%)	**Upadacitinib 15 mg QD (N=93) n (%)**
Male	69 (73%)	63 (68%)
Female	25 (27%)	30 (32%)
Age, years	43.7 (12.1)	47.0 (12.8)
Body-mass index, kg/m^2	26.9 (5.1)	26.6 (4.9)
Race		
White	76 (81%)	79 (85%)
Asian	16 (17%)	13 (14%)
African American	2 (2%)	1 (1%)
Region		
USA and Canada	10 (11%)	9 (10%)
Western Europe	33 (35%)	30 (32%)
Eastern Europe	34 (36%)	36 (39%)
Asia*	14 (15%)	12 (13%)
Australia and New Zealand	3 (3%)	6 (6%)
HLA-B27 positive	73 (78%)	70 (75%)
Duration since diagnosis, years	6.0 (6.8)	7.8 (10.6)
Duration since symptoms, years	14.0 (9.9)	14.8 (11.6)
Previous NSAID use	94 (100%)	92 (99%)†††
Concomitant NSAID use	81 (86%)	71 (76%)
Concomitant csDMARD use	17 (18%)	13 (14%)
Sulfasalazine	14 (15%)	8 (9%)
Mesalazine	1 (1%)	1 (1%)
Methotrexate	2 (2%)	4 (4%)
Hydroxychloroquine	0	1 (1%)
Concomitant glucocorticoid use	12 (13%)	6 (6%)
Back pain†	6.7 (1.8)	6.8 (1.8)
Patient global assessment of disease activity‡	6.8 (1.7)	6.6 (1.8)
Inflammation§	6.7 (1.9)	6.5 (2.0)
ASDAS‡	3.7 (0.7)	3.5 (0.8)

BASDAI**	6.5 (1.6)	6.3 (1.8)
BASFI‡	5.5 (2.2)	5.4 (2.4)
BASMI	3.5 (1.5)	3.7 (1.5)
MASES††	3.7 (2.7)	3.9 (2.8)
SPARCC MRI spine score §§	11.9 (14.5)	10.4 (14.4)
SPARCC MRI sacroiliac joint score‡‡	5.4 (8.6)	7.9 (10.9)
hsCRP, mg/L	11.7 (11.1)	9.6 (12.6)
hsCRP > ULN	68 (72%)	67 (72%)
ASQoL‡	10.3 (4.7)	10.0 (5.3)
WPAI overall work impairment***	53.3 (24.6)	54.3 (28.1)
ASAS Health index‡	8.2 (3.8)	8.6 (4.1)

Data are n (%) and mean (SD) unless otherwise noted.

ASAS: assessment of SpondyloArthritis international society; ASDAS: ankylosing spondylitis disease activity score; ASQoL: ankylosing spondylitis quality of life; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis metrology index; csDMARD: conventional synthetic disease-modifying antirheumatic drug; HLA-B27: human leukocyte antigen B27; hsCRP: high sensitivity C-reactive protein; MASAS: Maastricht ankylosing spondylitis enthesitis score; MRI: magnetic resonance imaging; NSAID: non-steroidal anti-inflammatory disease; QD: once a day; SPARCC: Spondyloarthritis Research Consortium of Canada; ULN: upper limit of normal; USA: United States of America; WPAI: work productivity and activity impairment;

* 13 patients from Japan (seven in placebo; six in upadacitinib; the other 13 patients from Asia were from South Korea

† 92 in the upadacitinib group; back pain defined on a numerical rating scale (0–10) based on the following question, “What is the amount of back pain that you experienced at any time during the last week?”

‡ 91 in the upadacitinib group.

§ 92 in the upadacitinib group. Inflammation defined as mean of items 5 and 6 of the BASDAI.

** 92 in the upadacitinib group.

†† Assessed in 55 in the placebo group; and 54 in the upadacitinib group with MASES >0 at baseline

§§ 81 in the placebo group; 84 in the upadacitinib group.

‡‡ 80 in the placebo group; 84 in the upadacitinib group.

*** Assessed in 66 in the placebo group and 64 in the upadacitinib group who were employed at baseline.

††† One patient did not have previous NSAID therapy due to contraindications to NSAID therapy (warfarin use due to history of deep venous thrombosis and pulmonary embolism approximately 10 years before entering the study).

Source: van der Heijde et al. (2019)[44]

B.3.6.1.6 Results: Analysis of ASAS40 at week 14 (primary endpoint)

More than half the patients who received upadacitinib achieved ASAS40 at week 14 (51.6%), which was a statistically significant improvement compared to those who received the placebo (25.5%) (**Table 14**). This translates as a 40% improvement in AS response and an absolute improvement in three of the four following domains: back pain, patient global assessment of

disease activity, physical function, and inflammation, which is a stringent measure of disease activity.

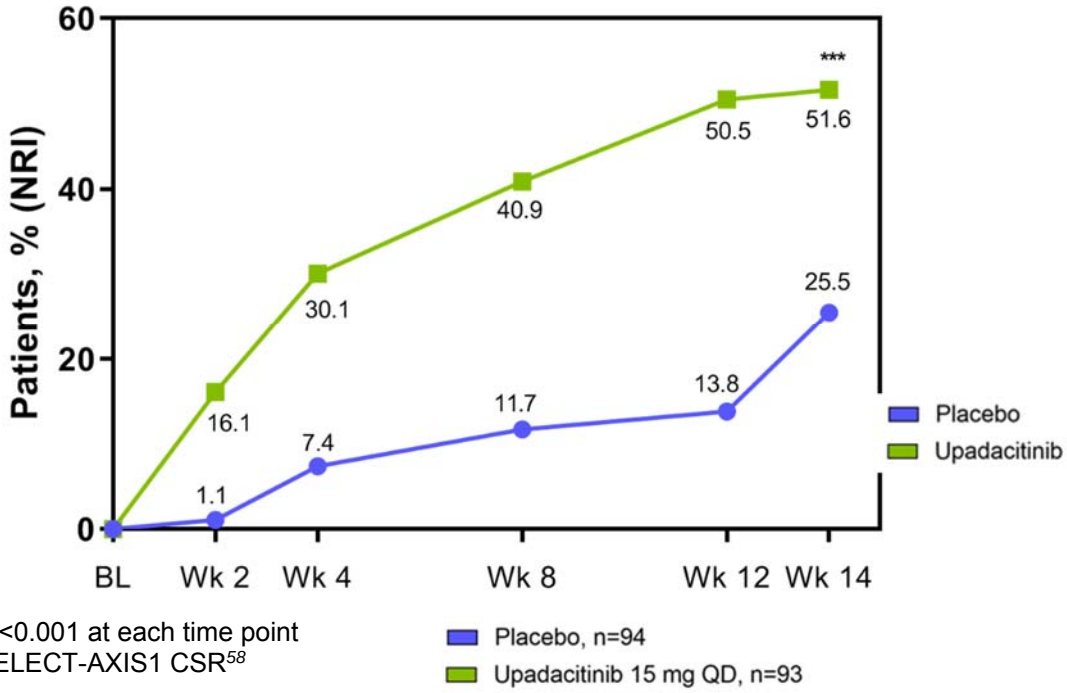
Differences between treatment groups in the proportion of patients who achieved ASAS40 were observed as early as week 2 (16.1% vs 1.1% in the upadacitinib arms and placebo arms, respectively) and at each measurement point up to week 14 (

Figure 4). Differences in the response rate at each time point achieved nominal P < 0.001.

Table 14. Analysis of ASAS40 at week 14

Treatment	Responder n	Response rate (95% CI)	Response rate difference (upadacitinib – placebo)	
			Point estimate (95% CI)	P-Value
Placebo (n = 94)	24	25.5 (16.7, 34.3)	26.1 (12.6, 39.5)	< 0.001
Upadacitinib 15 mg QD (n = 93)	48	51.6 (41.5, 61.8)		
CI: confidence interval; QD: once a day; Source: van der Heijde 2019[44]				

Figure 4. ASAS40 response rate by visit during Period 1



Nominal P<0.001 at each time point
Source: SELECT-AXIS1 CSR[58]

Placebo, n=94
Upadacitinib 15 mg QD, n=93

B.3.6.1.7 Results: Key secondary endpoints

Results from the key secondary endpoints were consistent with the primary endpoint (Table 15). Accounting for multiplicity adjustment, changes from baseline to Week 14 in ASDAS (CRP), SPARCC MRI spine, and BASFI, and proportion of subjects who had BASDAI50 and an ASAS partial remission were statistically significant for upadacitinib versus placebo. Improvements were also demonstrated for MASES and BASMI at Week 14, with nominal P-values < 0.05.

A more detailed breakdown of the clinical endpoints from SELECT-AXIS1 is provided in Appendix B.

Table 15. Summary of ranked secondary efficiency endpoint results at week 14

Endpoint	N	Within group point estimate (95% CI)	Between group difference (Upadacitinib – placebo)		
			Point estimate (95% CI)	Nominal P-Value	Multiplicity adjusted results
ASDAS (CRP) change from baseline					
Placebo	84	[redacted]	[redacted]	<0.001	Significant
Upadacitinib	84	[redacted]			
SPARCC Score – Spine, change from baseline					
Placebo	60	[redacted]	[redacted]	<0.001	Significant
Upadacitinib	68	[redacted]			
BASDAI50 response rate					
Placebo	94	[redacted]	[redacted]	0.002	Significant
Upadacitinib	93	[redacted]			
ASQoL change from baseline					
Placebo	88	[redacted]	[redacted]	0.016	Non-significant
Upadacitinib	88	[redacted]			
ASAS partial remission response rate					
Placebo	94	[redacted]	[redacted]	< 0.001	Significant
Upadacitinib	93	[redacted]			
BASFI change from baseline					
Placebo	86	[redacted]	[redacted]	0.001	Significant
Upadacitinib	86	[redacted]			
BASMI change from baseline					
Placebo	89	[redacted]	[redacted]	0.030	Non-significant
Upadacitinib	89	[redacted]			
MASES (for subjects with baseline enthesitis) change from baseline					
Placebo	51	[redacted]	[redacted]	0.049	Non-significant
Upadacitinib	50	[redacted]			
WPAI overall work impairment change from baseline					
Placebo	53	[redacted]	[redacted]	0.190	Non-significant
Upadacitinib	55	[redacted]			
ASAS health index change from baseline					
Placebo	88	[redacted]	[redacted]	0.007	Non-significant
Upadacitinib	88	[redacted]			

ASAS: assessment of ankylosing spondylitis; ASDAS: ankylosing spondylitis disease activity score; ASQoL: ankylosing spondylitis quality of life; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis mobility index; CI: confidence interval; CRP: c-reactive protein; MASES: Maastricht ankylosing spondylitis enthesitis score; SPARCC: Spondyloarthritis Research Consortium of Canada; WPAI: work productivity and activity impairment questionnaire.

Source: SELECT-AXIS1 CSR[58]

B.3.6.2 SELECT-AXIS2, Study 1: bDMARD-IR AS patients

Key points from SELECT-AXIS2, Study 1

- Significantly more patients achieved ASAS40 treatment response in the upadacitinib arm compared to the placebo arm at week 14 (44.5% vs 18.2%).[66] Upadacitinib showed onset of effect in ASAS40 as early as week 4.
- A significant improvement was also seen in all ranked secondary endpoints (all p<0.0001).
- The safety profile of upadacitinib was consistent with SELECT-AXIS1 and no new risks were identified.
- The rate of adverse events was similar between the two treatment groups ([redacted]% in the upadacitinib arm versus [redacted]% in the placebo arm).
- Results from SELECT-AXIS2 support the option for patients with active AS to be treated with upadacitinib.

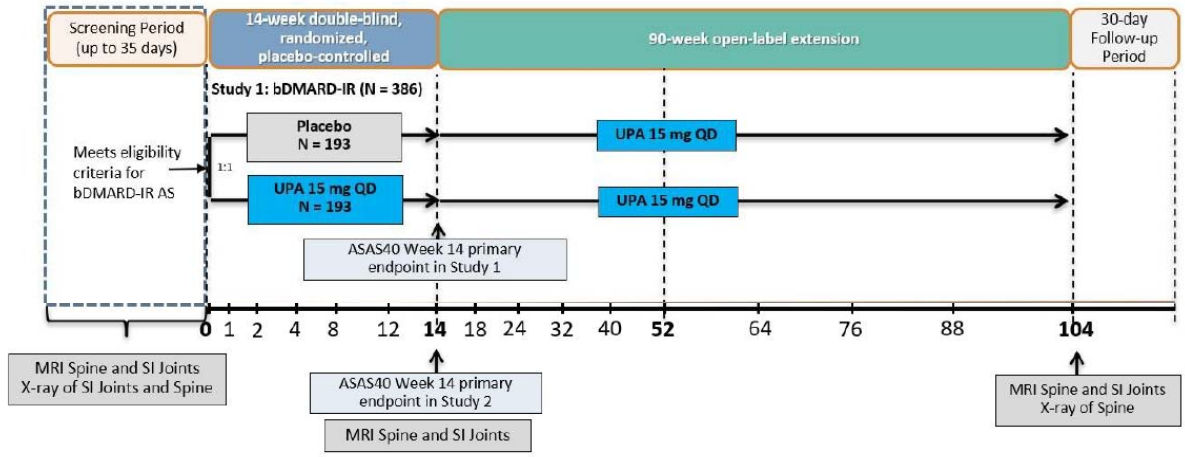
B.3.6.2.1 Study design

SELECT-AXIS2, Study 1 is a phase 3 multicentre, randomised, double-blind, placebo-controlled, two-period, parallel-group study whose primary objective was to demonstrate the safety and efficacy of upadacitinib in patients with active AS who are bDMARD-IR.

Patients were randomised (1:1) to receive oral upadacitinib 15 mg once daily or oral placebo for 14 weeks (Period 1). Patients who completed Period 1 entered Period 2: an open-label extension to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD over 90 weeks, which is currently ongoing, and therefore, only results from Period 1 are currently available. The study design of SELECT-AXIS2 is described in

. A summary of the methodology for SELECT-AXIS2 is provided in Table 16. The sections that follow give additional information on eligibility criteria (Section B.3.6.1.3) and statistical methods (Section B.3.6.1.4).

Figure 5. Study design of SELECT-AXIS2 Study 1



AS: ankylosing spondylitis; ASAS: Assessment of SpondyloArthritis International Society; bDMARD-IR: biologic disease-modifying antirheumatic drug inadequate responder; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; QD: once daily; SI: sacroiliac; UPA: upadacitinib.

Source: Adapted from the SELECT-AXIS2 protocol[59]

Table 16. Summary of trial methodology - SELECT-AXIS2

Trial name	SELECT-AXIS2 (NCT 04169373)
Location	North America, South America, Australia and New Zealand, Europe, Asia,
Trial design	Phase 3 multicentre, randomised, double-blind, placebo-controlled, two-period, parallel-group
Eligibility criteria for participants	Adults with active AS, who fulfilled modified New York criteria, previously treated with 1 or 2 bDMARDs and had inadequate response or intolerance. Additional details are provided in Table 17.
Settings and locations where data were collected	The study was conducted in 119 academic centres and hospitals in 22 countries across North America, South America, Australia and New Zealand, Europe and Asia. This included 4 UK centres.
Study drugs	Upadacitinib 15 mg QD Oral placebo
Concomitant medications	Patients could continue their stable background csDMARD therapy, restricted to MTX, SSZ, hydroxychloroquine, chloroquine, apremilast and leflunomide, throughout the study. A combination of up to two background csDMARDs was allowed except for the combination of MTX and leflunomide. Patients entering the study on concomitant oral corticosteroids, must be on a stable dose of prednisone (≤ 10 mg/day) or oral corticosteroid equivalent for at least 14 days prior to the baseline visit. If entering the study on concomitant NSAIDs, tramadol, combination of acetaminophen/ paracetamol and codeine or combination of acetaminophen/ paracetamol and hydrocodone, and/or non-opioid analgesics, patients must be on stable dose(s) for at least 14 days prior to the baseline visit.

Trial name	SELECT-AXIS2 (NCT 04169373)
	The following concomitant medications or therapies were not permitted at any time during the study: • Any JAK inhibitor • Intra-articular joint injections, spinal/paraspinal injections or parenteral administration of corticosteroids • Opioid analgesics, except for the combination of acetaminophen/paracetamol and codeine or acetaminophen/paracetamol and hydrocodone, • Live vaccines • Strong CYP3A inhibitors or inducers • Investigational drugs
Primary outcome	The proportion of patients with ASAS 40 response at Week 14, defined as a ≥ 40% improvement and an absolute improvement of ≥ 2 units (on a scale of 0 to 10) from baseline in at least three of the following four domains, with no worsening in the remaining domain: • Patient's Global Assessment – represented by the PtGA NRS score (0 to 10); • Pain – represented by the Patient's Assessment of Total Back Pain NRS score (0 to 10); • Function – represented by the BASFI NRS score (0 to 10); • Inflammation – represented by the mean of the two morning stiffness-related BASDAI NRS scores (mean of items 5 and 6 of the BASDAI [0 to 10]).
Other outcomes specified in the scope	Disease activity: • Change from baseline in ASDAS • 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 major improvement (a change from baseline of ≤ -2.0) • ASDAS Inactive Disease (ASDAS score < 1.3) • ASDAS Low Disease Activity (ASDAS score < 2.1) • ASDAS Major Improvement (change from baseline at least 2.0) • ASDAS Clinically Important Improvement (change from baseline of at least 1.1) • Change from baseline in BASDAI Functional capacity: • Change from baseline in BASFI • Change from baseline in $BASMI_{lin}$ 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

Trial name	SELECT-AXIS2 (NCT 04169373)
	• Change from baseline in Patient's assessment of nocturnal back pain Peripheral symptoms: • Change from baseline in MASES Adverse events HRQoL: • Change from baseline in ASQoL • Change from baseline in WPAI
Pre-planned subgroups	Pre-specified subgroup analyses based on baseline disease characteristics and stratification factors is planned after study completion.
AS: ankylosing spondylitis; 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; FACIT-F: Functional assessment of chronic illness therapy - fatigue; HI: health index; ISI: insomnia severity 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; SJC: swollen joint count; SPARCC: spondyloarthritis research consortium of Canada; SSZ: sulfasalazine; TJC: tender joint count; UK: United Kingdom; WPAI: work productivity and activity impairment; Source: SELECT-AXIS2 protocol[59]	

B.3.6.2.2 Study treatments

Two groups of patients were randomised 1:1 to receive either upadacitinib 15 mg QD or oral placebo for 14 weeks (Period 1) (**Figure 5**). At week 14, all patients either continued or switched to upadacitinib 15 mg QD for a further 90 weeks (Period 2). Period 2 is still ongoing and so only data from Period 1 is presented.

B.3.6.2.3 Eligibility criteria

Key eligibility criteria for patients in SELECT-AXIS2 are provided in Table 17.

Table 17. Key inclusion and exclusion criteria for SELECT-AXIS2

Key inclusion criteria	Key exclusion criteria
• Patient must be an adult male or female, at least 18 years of age at screening • Patient must have a clinical diagnosis of AS and patients must meet the modified New York criteria for AS. • Patient must not have total spinal ankylosis. • Patient must meet the following scores at Screening and Baseline Visits: BASDAI score ≥ 4 and Total Back Pain score ≥ 4 based on a 0 – 10 NRS. • Patient must have been previously exposed to 1 or 2 bDMARDs (TNFI or IL-17A inhibitor), and the patient must have discontinued the bDMARD therapy due to either lack of efficacy (after at least 12 weeks of treatment with a bDMARD at an adequate dose) or intolerance (irrespective of treatment duration). Prior exposure to a 2nd bDMARD is allowed for no more than 30% of patients. Patients who have had lack of efficacy to 2 bDMARDs (including both a TNF inhibitor and IL-17 inhibitor) are not eligible. For further details, see the study protocol[59]	• Patient must not have been exposed to Janus Kinase (JAK) inhibitor. • Prior bDMARD therapy has to be washed out. • Patient must not have a history of an allergic reaction or significant sensitivity to constituents of the study drug. For further details, see the study protocol[59]
AS: ankylosing spondylitis; BASDAI: Bath ankylosing spondylitis disease activity index; bDMARDs: biologic disease-modifying antirheumatic drugs; IL: interleukin; JAK: Janus kinase; NRS: numerical rating scale; TNF: tumour necrosis factor, Source: SELECT-AXIS1 protocol[59]	

B.3.6.2.4 Statistical analysis and definition of study groups

A summary of the statistical analysis of SELECT-AXIS2 is provided in Table 18.

Table 18. Statistical analysis and definition of study groups in SELECT-AXIS2

	SELECT-AXIS2 (NCT 04169373)
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	The primary efficacy analysis will use the composite estimate framework, where the Week 14 primary endpoint for both studies is defined as a composite endpoint that is achieved if a patient fulfils 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. Corresponding to this estimate, in the primary analysis, patients who discontinue study drug prior to Week 14 will be treated 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 will be 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-AXIS2 CSR[59]	

B.3.6.2.5 Patient disposition and baseline characteristics

Patient disposition

A total of 420 patients were randomised in SELECT-AXIS2 study 1 and received treatment, of which 409 (97.4%) completed treatment through week 14. The rates of premature discontinuation were low and similar between the placebo group and the upadacitinib treatment group (Table 19).

Table 19. Patient disposition in SELECT-AXIS2

	Placebo, n (%)	Upadacitinib 15 mg QD, n (%)
Patient status		
Randomised	[redacted]	[redacted]
Completed	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]
Reasons for discontinuations		
Adverse events	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
COVID-19 infection	[redacted]	[redacted]
COVID-19 logistical restrictions	[redacted]	[redacted]
Other	[redacted]	[redacted]
QD: once per day; Source: SELECT-AXIS2 CSR[59]		

Baseline characteristics

The baseline characteristics were balanced across the treatment groups and consistent with the targeted patient population (Table 20, Section 3.6).

The mean age was similar in both groups (placebo: [redacted]; upadacitinib: [redacted]). The majority of patients were male (placebo: [redacted]%; upadacitinib: [redacted]%) and the majority were of white race (placebo: [redacted]%; upadacitinib: [redacted]%). Disease duration since diagnosis and the time from appearance of symptoms was similar in both treatment arms, ([redacted] and [redacted] years since diagnosis and [redacted] and [redacted] years since the appearance of symptoms, in the placebo and upadacitinib treatment arms, respectively). This difference in the duration between the onset of symptoms and diagnosis is due to an average diagnostic delay of 8.57 years observed in patients with AS.[16,17]

Table 20. Baseline characteristics of patients in SELECT-AXIS2

	Placebo (N=209) n (%)	**Upadacitinib 15 mg QD (N=211) n (%)**
Male	[redacted]	[redacted]
Age, years	[redacted]	[redacted]
White	[redacted]	[redacted]
Region		
USA and Canada	[redacted]	[redacted]
South/Central America	[redacted]	[redacted]
Western Europe	[redacted]	[redacted]
Eastern Europe	[redacted]	[redacted]
Asia[a]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]
HLA-B27 positive	[redacted]	[redacted]
Duration since diagnosis, years	[redacted]	[redacted]
Duration since symptoms, years	[redacted]	[redacted]
NSAID use at baseline	[redacted]	[redacted]
Oral corticosteroids at baseline	[redacted]	[redacted]
csDMARD use at baseline	[redacted]	[redacted]
Prior bDMARD use class		
1 TNFi	[redacted]	[redacted]
1 IL-17A inhibitor	[redacted]	[redacted]
2 bDMARDs exposure	[redacted]	[redacted]

BASDAI (0-10)	[redacted]	[redacted]
Total back pain (NRS 0-10)	[redacted]	[redacted]
Nocturnal back pain (NRS 0-10)	[redacted]	[redacted]
Patient global assessment (NRS 0-10)	[redacted]	[redacted]
ASDAS (CRP)	[redacted]	[redacted]
BASFI (Function) (0-10)	[redacted]	[redacted]
BASMI (Mobility)	[redacted]	[redacted]
Presence of enthesitis at baseline (MASES >0)	[redacted]	[redacted]
MASES Score (0-13)[c]	[redacted]	[redacted]
MRI spine SPARCC (0-108)[d]	[redacted]	[redacted]
MRI sacroiliac joint SPARCC (0-72)[d]	[redacted]	[redacted]
hsCRP at screening (mg/L)	[redacted]	[redacted]
hsCRP > ULN (2.87mg/L) at screening	[redacted]	[redacted]
ASQoL (0-18)	[redacted]	[redacted]
ASAS Health index (0-17)	[redacted]	[redacted]

Data are n (%) and mean (SD) unless otherwise noted.

[a] China, Taiwan, South Korea and Japan; [b] New Zealand, Australia and Israel; [c] Summarised for patients with presence of enthesitis at baseline; [d] Summarised for patients with available baseline MRI data up to 3 days post first dose of study drug. ASDAS: Ankylosing spondylitis disease activity score; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis mobility index; bDMARD: biologic disease modifying antirheumatic drug; CRP: C-reactive protein; csDMARD: conventional synthetic disease modifying antirheumatic drug; IL-17: interleukin-17; MASES: Maastricht ankylosing spondylitis enthesitis score; MRI: magnetic resonance imaging; NRS: numerical rating scale; NSAID: non-steroidal anti-inflammatory drug; SPARCC: Spondyloarthritis Research Consortium of Canada; TNF: tumour necrosis factor. Source: SELECT AXIS2 CSR[65]

B.3.6.2.6 Efficacy results

The primary endpoint was achievement of ASAS40 response at week 14. The primary analysis using non-responder imputation in conjunction with multiple imputation (NRI-MI) to handle missing data due to COVID-19, showed a statistically higher response rate ($p > 0.0001$) in the upadacitinib group (44.5%) compared to the placebo group (18.2%).[66]

Figure 6 shows ASAS40 response rate over time up to week 14. Upadacitinib showed onset of effect in ASAS40 as early as week 4.

All ranked secondary endpoints were statistically significant (all $p < 0.0001$, Table 21).

Table 21. Primary and ranked key secondary efficacy endpoints at week 14

		Endpoint	Placebo n=209	Upadacitinib 15mg QD n-211	Upadacitinib – Placebo (95% CI)	P-Value[a]
Primary		ASAS40	18.2%	44.5%	[redacted]	<0.0001*
Ranked key secondary endpoints	1	ASDAS (CRP)	[redacted]	[redacted]	[redacted]	<0.0001*
	2	MRI Spine SPARCC[b]	[redacted]	[redacted]	[redacted]	<0.0001*
	3	BASDAI50	[redacted]	[redacted]	[redacted]	<0.0001*
	4	ASAS20	[redacted]	[redacted]	[redacted]	<0.0001*
	5	ASDAS (CRP) inactive disease	[redacted]	[redacted]	[redacted]	<0.0001*
	6	Total back pain	-1.47	-3.00	[redacted]	<0.0001*
	7	Nocturnal back pain	[redacted]	[redacted]	[redacted]	<0.0001*
	8	ASDAS (CRP) low disease activity	[redacted]	[redacted]	[redacted]	<0.0001*
	9	BASFI (Function)	-1.09	-2.26	[redacted]	<0.0001*
	10	ASAS partial remission	[redacted]	[redacted]	[redacted]	<0.0001*
	11	ASQoL	[redacted]	[redacted]	[redacted]	<0.0001*
	12	ASAS Health Index	[redacted]	[redacted]	[redacted]	<0.0001*
	13	BASMI (Mobility)	[redacted]	[redacted]	[redacted]	<0.0001*
	14	MASES (enthesitis)[c]	[redacted]	[redacted]	[redacted]	<0.0001*

Results for binary endpoints are based on NRI-MI analysis. Analyses for all continuous endpoints are for the change from baseline value. Results for continuous endpoints are based on MRMM, except for MRI and BASMI which use ANCOVA analysis.

a Unadjusted p-values are presented. * denotes multiplicity-controlled statistical significance at the pre-specified two sided 0.05 level.

b Summarised for patients with available baseline MRI data up to 3 days post first dose of study drug and available wee 14 MRI data up to the first dose of open-label period study drug

c Summarised for patients with presence of enthesitis at baseline (n=162 in placebo arm; n=148 in upadacitinib arm).

ASAS: assessment of ankylosing spondylitis; ASDAS: ankylosing spondylitis disease activity score; ASQoL: ankylosing spondylitis quality of life; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis metrology index; CI: confidence interval; CRP: C-reactive protein; MASES: Maastricht ankylosing spondylitis enthesitis score; MRI: magnetic resonance imaging; SPARCC: Spondyloarthritis Research Consortium of Canada;

Source: SELECT-AXIS2 CSR,[65] AbbVie press release 2021[66]

Figure 6. ASAS40 response rate by visit during Period 1

Nominal P ≤ 0.05 starting from Week 4

Source: SELECT-AXIS2 CSR[65]

B.3.7 Subgroup analysis

B.3.7.1 Subgroup analysis from SELECT-AXIS1

Pre-specified subgroups included in the analysis were age (<40, 40-65, ≥65), gender (male, female), BMI (<25, ≥25,), race (white, non-white), geographic region (North America, Europe, Other) and hsCRP level at screening (≤ULN, > ULN).

Treatment effects in all pre-specified subgroups were consistently in favour of upadacitinib compared to the placebo when considering the ASAS40 response at week 14 across all studied subgroups.[67]

B.3.8 Meta-analysis

A network meta-analysis (NMA) was conducted to estimate the relative effectiveness of upadacitinib and relevant comparator therapies (Section B.3.9).

B.3.9 Indirect and mixed treatment comparisons

Key points

- No direct trial-based comparisons of upadacitinib to relevant comparators were identified; therefore Bayesian NMAs were conducted to compare the relative effectiveness of upadacitinib and its comparators.
- NMAs in bDMARD-naïve and bDMARD-experienced patients are of particular relevance to the decision problem, demonstrating no significant differences between upadacitinib and all TNFi and IL-17A inhibitors across ASAS40, BASDAI50, BASDAI CFB and BASFI CFB outcomes.
- These findings are further supported by a comprehensive, robust and wide range of supplementary analyses which present results using alternative trial time points, random or fixed effects models, adjusted or unadjusted NMA, and additional variables.
- Overall, upadacitinib has comparable efficacy to all TNFi and IL-17A inhibitors assessed for the treatment of active AS.
- The conclusions from the NMA confirm that a cost-comparison analysis is the appropriate format for the economic evaluation.

Network meta-analyses (NMAs) were undertaken to compare the relative efficacy between alternative treatments, TNFi and IL-17A inhibitors, in patients with active AS after 12 to 16 weeks of treatment. The 12-16 week timepoint was identified to reflect the recommended timepoint to assess treatment response.[2,29] Therefore, for a given outcome the inputs into the NMA may have differed between interventions in terms of the timepoint considered. However, use of trial primary endpoints was considered to be the most robust approach to estimating true relative treatment effects. Data are available considering both the week 12 and week 14 (primary endpoints) from the SELECT-AXIS1 and 2 trials. The most relevant analyses to the current decision problem are summarised below and reported in full, along with the corresponding methods, in the NMA report (Appendix D).

Treatment history has an observed impact on subsequent efficacy, and therefore, it is considered inappropriate to conduct an 'all patients' NMA for any outcome.[31,43] bDMARD experience was reflected in NMA analyses during the most recent NICE appraisal of ixekizumab,[6,7] in which the company submitted separate NMAs for biologic naïve and experienced populations aligned to its clinical trial populations, rather than relying on sensitivity analysis from a mixed population. This approach was deemed appropriate and has

been applied to the current NMA methodology in this submission, where separate networks have been constructed to reflect bDMARD experience, referred to as bDMARD-naïve and bDMARD-IR (experienced).

Aligned with the NICE scope, all eligible comparators are considered within the NMA. However, it should be noted that the bDMARD-IR NMA only includes ixekizumab, due to the limited availability of high quality evidence available describing secukinumab (Section **Error! Reference source not found.**).The MEASURE trials studying the efficacy of secukinumab were not considered suitable for inclusion in the bDMARD-IR NMA due to small patient population who were bDMARD-IR. Similarly, the inclusion criteria for bDMARD-IR patients in MEASURE1 and 2 differed from that used during the SELECT-AXIS2 trial, where patients who were exposed to 2 or more bDMARDs were excluded from MEASURE1 and 2 whereas patients were required to have been exposed to 1 or 2 prior bDMARDs in SELECT-AXIS2, and therefore, these patients populations were not considered directly comparable. Based on clinician feedback, the comparison between the efficacy of upadacitinib and secukinumab is likely to be similar in the bDMARD-naïve and bDMARD-experienced populations. A scenario analysis is presented in Appendix D, Sections 7.2 and 7.5 that includes all secukinumab evidence available.

The following results are described in the submission for the bDMARD-naïve and bDMARD-IR NMAs and the rationale for presenting these results is as follows:

- 14 week timepoint for upadacitinib is used as this aligns with the primary outcome of the SELECT-AXIS1 and SELECT-AXIS2 trials and reflects the recommended timepoint to assess treatment response.[2,29]

- Results for ASAS40, BASDAI50, BASDAI CFB and BASFI CFB are presented given that these variables either reflect the primary outcome of SELECT-AXIS1 and SELECT-AXIS2 trials, or are key clinical endpoints recommended by the BSR guidelines for to assess AS activity.[68]

- The preferred model is presented and is dependant on model fit, either fixed or random effects, with or without baseline risk adjustment.

A comprehensive, robust and wide range of supplementary analyses which consider alternative trial time points, random or fixed effects models, placebo adjusted or unadjusted NMA, and additional variables, including CRP and age, are available in Appendix D, Section 7.6 and 7.7. CRP was explored in a recent NMA due to RCTs commonly reporting this

endpoint and was investigated as a marker for change in active inflammation.[47] Moreover, based on expert feedback, CRP and age were identified as potential covariates of interest for exploring in the indirect comparison. Note, due to the limited data available for the bDMARD-IR network it was not possible to make adjustments for age and CRP in this population.

Overall, the results presented within the submission and in Appendix D demonstrate that upadacitinib is equivalent in terms of clinical efficacy versus all relevant comparators included within the scope of the decision problem, including secukinumab and ixekizumab. A summary of the NMA conducted is provided in .

Table 22.

Table 22. Summary of NMA inputs

		Primary analysis	Scenario analysis	Rationale
Treatment history		Population stratified by treatment history	Not applicable	This approach is in line with previous AS HTAs and evidence describing impact of prior biologic on treatment outcomes
Comparators	DMARD-naïve	All relevant comparators: TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) and IL17A inhibitors (secukinumab and ixekizumab)	Not applicable	As per NICE scope
	DMARD-IR	Evidence sought for all comparators, but comparison versus ixekizumab only	Comparison versus ixekizumab and secukinumab	Robust evidence was identified for ixekizumab only. A scenario analysis was conducted including secukinumab, but this was limited by small patient population, as well as difference in patient population and study design (see Section B.3.9.1.1.2)
Outcomes		ASAS40, BASDAI50, BASDAI CFB and BASFI CFB	Not applicable	This aligns with NICE scope, previous AS HTAs and BSR guidelines
Outcome definition	Upadacitinib	14 weeks	16 weeks	This aligns with the endpoint definition within SELECT-AXIS1 and SELECT-AXIS2
	TNFi	12 weeks	Not applicable	Available outcomes are limited to those in the published literature.
	Secukinumab and ixekizumab	16 weeks	Not applicable	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 D.		The rationale for primary analysis is documented in Appendix D
		Placebo-adjusted and unadjusted outcomes are presented; rationale for primary analysis is documented in Appendix D.		The rationale for primary analysis is documented in Appendix D

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

A systematic literature review was performed to identify potentially relevant studies for potential inclusion in the NMAs (see Appendix C for details).

Initial searches were conducted in March 2021. A total of 191 articles were included in the review, reporting 63 unique RCTs to be considered for inclusion in the NMAs. Only studies that reported relevant week 12 to 16 outcomes were used. Conference abstracts with subsequent full-text publications available were not considered for inclusion in the NMAs. Therefore, 32 records ultimately contributed data for the 24 RCTs included in the NMAs (see Figure 7 and Appendices C and D for detail). Excluded studies are summarised in Appendix C.

B.3.9.1.1.2 Overview of selected studies

In terms of study selection, the comparators of interest to upadacitinib are TNFi (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) or IL-17A inhibitors (secukinumab and ixekizumab).

The SELECT-AXIS1 trial, which compares upadacitinib 15 mg QD with placebo in patients with active AS who have not received prior bDMARD treatment, was used to inform the analysis for the naïve population. The SELECT-AXIS2 trial, study 1 which included patients with AS who had failed a previous bDMARD (bDMARD-IR) was used to inform the analysis for the bDMARD-IR population.

An overview of the 26 RCTs (including SELECT-AXIS 2, which has not yet been published, and is thus not included in the SLR) included in the NMA is presented in Table 23 below, along with their primary and secondary (if any) sources used.

Table 23. Overview of RCTs included from the clinical SLR

Study	Intervention arm(s)	Comparator arm(s)	Study design	bDMARD experience	Total N	Duration of randomized phase (weeks)	Primary endpoint	Primary (secondary) reference(s) used
ASSERT (NCT00207701)	Infliximab, 5 mg/kg, IV infusion,	Placebo, IV infusion,	Phase 3 # treatment arms: 2 # centres: 33 Randomisation 8:3 Blinding: Double	Mixed (no anti-TNF other than INF within 3 months of screening; no INF at any time)	279	24	ASAS20 @ Week 24	van der Heijde 2005[69] (Braun 2008[70])
ATLAS (NCT00085644)	Adalimumab, 40 mg, SC injection	Placebo, SC injection,	Phase 3 # treatment arms, 2 # centres, 43 Randomisation, 2:1 Blinding: Double	Naïve	315	12	ASAS20 @ Week 12	van der Heijde 2006[71]
Bao 2014 (NCT01248793)	Golimumab, 50 mg, SC injection	Placebo, SC injection,	Phase 3 # treatment arms: 2 # centres: 12 Randomisation: 1:1 Blinding: Double	Naïve	213	16	ASAS20 @ Week 14	Bao 2014[72]
Barkham 2010	Etanercept, 25 mg, SC injection	Placebo, SC injection	Phase NR '# treatment arms: 2 # centres: 1 Randomisation: 1:1 Blinding: Double	NR (assumed mixed, majority naïve)	40	12	Change in the work instability of patients (AS-WIS) @ week 12	Barkham 2010[73]
Braun 2002	Infliximab, 5 mg/kg at weeks	Placebo, IV infusion	Phase NR # treatment arms: 2 # centres: NR Randomisation: 1:1 Blinding: Double	Naïve (assumed as bDMARDs were likely not yet available*)	70	12	BASDAI50 @ Week 12	Braun 2002[74]
Calin 2004 (NCT00421915; 0881A3-311-EU)	Etanercept, 25 mg, SC injection	Placebo, SC injection	Phase 3 # treatment arms, 2 # centres, 14 Randomisation, 1:1 Blinding: Double	Naïve	84	12	ASAS 20 @ Week 12	Calin 2004[75] (Dijkmans 2009[76])

Study	Intervention arm(s)	Comparator arm(s)	Study design	bDMARD experience	Total N	Duration of randomized phase (weeks)	Primary endpoint	Primary (secondary) reference(s) used
COAST-V (NCT02696785)	Ixekizumab, 80 mg	Placebo or Adalimumab 40 mg,	Phase 3 # treatment arms, 4 # centres, 84 Randomisation, 1:1:1:1 Blinding: Double	Naïve	341	16	ASAS40 @ Week 16	van der Heijde 2018[77] (Dougados 2020[78], CADTH IXE Clinical Review Report[79])
COAST-W (NCT02696798)	Ixekizumab, 80 mg Q2W or 80 mg Q4W, SC injections;	Placebo, SC injections,	Phase 3 # treatment arms, 3 # centres, 106 Randomisation, 1:1:1 Blinding: Double	Prior: discontinued at least 1 TNFi, but no more than 2 TNFi, either due to intolerance or due to an IR to treatment with a single TNFi for at least 12 weeks at an adequate dose	316	16	ASAS40 @ Week 16	Deodhar 2019[80] (Dougados 2019[78])
Davis 2003	Etanercept, 25 mg, SC,	Placebo, SC,	Phase NR # treatment arms: 2 # centres: 28 Randomisation: 1:1 Blinding: Double	Naïve	277	24	ASAS20 @ Week 12	Davis 2003[81]
GO-RAISE (NCT00265083)	Golimumab, 50 mg or 100 mg, SC injection,	Placebo, SC injection,	Phase 3 # treatment arms: 3 # centres: 57 Randomisation: 1:1.8:1.8 Blinding: Double	Naïve	356	16	ASAS20 @ Week 14	Inman 2008[82]
Gorman 2002	Etanercept, 25 mg,	Placebo, SC injection	Phase NR # treatment arms: 2 # centres: NR Randomisation: 1:1 Blinding: Double	Naïve (assumed as bDMARDs were likely not yet available*)	40	16	ASAS20 @ Week 16	Gorman 2002[83]
Hu 2012	Adalimumab, 40 mg	Placebo	Phase NR # treatment arms: 2 # centres: 1 Randomisation: 1:1 Blinding: Double	NR (assumed mixed, majority naïve)	46	12	CFB in BASDAI, BASFI, CRP, ASDAS MRI of lumbar spine and sacroiliac joints, and lumbar spine FDL @ week 12	Hu 2012[84]

Study	Intervention arm(s)	Comparator arm(s)	Study design	bDMARD experience	Total N	Duration of randomized phase (weeks)	Primary endpoint	Primary (secondary) reference(s) used
Huang 2014 (NCT01114880)	Adalimumab, 40 mg,	Placebo, SC injection	Phase 3 # treatment arms: 2 # centres: 9 Randomisation: 2:1 Blinding: Double	Naïve	344	12	ASAS20 @ Week 12	Huang 2014[85]
M03-606 Canadian AS Study (NCT00195819)	Adalimumab, 40 mg,	Placebo, SC injection	Phase 3 # treatment arms: 2 # centres: 11 Randomisation: 1:1 Blinding: Double	Naïve	82	24	ASAS20 @ Week 12	Lambert 2007[86] (Maksymowych 2008[87])
MEASURE 1 (NCT01358175 (ext NCT01863732))	Secukinumab, 10 mg/kg (IV loading dose) followed by SC injections of 150 mg or 75 mg	Placebo, IV and then SC injections	Phase 3 # treatment arms, 3 # centres, 65 Randomisation, 1:1:1 Blinding: Double	Mixed (previous use of anti-TNFs allowed, but washout period required) - Data for naïve and IR subgroups available	371	16	ASAS20 @ Week 16	Baeten 2015[43] (Deodhar 2016[88])
MEASURE 2 (NCT01649375)	Secukinumab, 150 mg or 75 mg,	Placebo, SC injection	Phase 3 # treatment arms: 3 # centres: 53 Randomisation: 1:1:1 Blinding: Double	Mixed (previous use of anti-TNFs allowed, but washout period required) - Data for naïve and IR subgroups available	219	16	ASAS20 @ Week 16	Baeten 2015[43] (Sieper 2017[89]; Deodhar 2019[90]; Marzo-Ortega 2019[91])
MEASURE 3 (NCT02008916)	Secukinumab, 10 mg/kg IV loading dose, followed by secukinumab 300 mg or 150 mg, SC injections	Placebo, IV infusion followed by SC injections,	Phase 3 # treatment arms, 3 # centres, 54 Randomisation, 1:1:1 Blinding: Double	Mixed (previous use of anti-TNFs allowed, but washout period required) - Data for naïve and IR subgroups available	226	16	ASAS20 @ Week 16	Pavelka 2017[63]
MEASURE 4 (NCT02159053)	Secukinumab, 150 mg, with or without loading dose, SC injections	Placebo, SC injection,	Phase 3 # treatment arms: 3 # centres: 85 Randomisation: 1:1:1 Blinding: Double	Mixed (previous use of anti-TNFs allowed, but washout period required) - Data for naïve and IR subgroups available	350	16	ASAS20 @ Week 16	Kivitz 2018[92]

Study	Intervention arm(s)	Comparator arm(s)	Study design	bDMARD experience	Total N	Duration of randomized phase (weeks)	Primary endpoint	Primary (secondary) reference(s) used
MEASURE 5 (NCT02896127)	Secukinumab, 150 mg, SC injection	Placebo, SC	Phase 3 # treatment arms, 2 # centres, NR Randomisation, 2:1 Blinding: Double	Mixed (previous use of anti-TNFs allowed, but washout period required) - Data for naïve and IR subgroups available	458	16	ASAS20 @ Week 16	Huang 2020[93]
Pedersen 2016 (NCT00477893)	Adalimumab, 40 mg, SC,	Placebo, SC,	Phase 4 # treatment arms, 2 # centres, 7 Randomisation, 1:1 Blinding: Double	Naïve	52	12	BASDAI50 @ Week 24	Pedersen 2016[94]
RAPID-axSpA (NCT01087762) (AS sub-population)	Certolizumab pegol, 400 mg	Placebo, 0.9% saline,	Phase 3 # treatment arms, 3 # centres, 83 Randomisation, 1:1:1 Blinding: Double	Mixed (≤2 previous bDMARDs)	178	16	ASAS20 @ Week 12	Landewe 2014[95]
SELECT-AXIS 1 (NCT03178487)	Upadacitinib, 15 mg, oral	Placebo, oral,	Phase 2/3 # treatment arms, 2 # centres, 62 Randomisation, 1:1 Blinding: Double	Naïve	187	14	ASAS40 @ Week 14	van der Heijde 2019[44] (Data on file[96])
SELECT-AXIS 2, (NCT04169373) (AS bDMARD-IR sub-population)	Upadacitinib, 15 mg, oral,	Placebo, oral,	Phase 3 # treatment arms, 2 # centres, 212** Randomisation, 1:1 Blinding: Double	Previously exposed to 1 or 2 bDMARDs, discontinued due to either IR or intolerance	420	14	ASAS40 @ Week 14	Data on file[97]
SPINE (NCT00420238)	Etanercept, 50 mg, SC injection,	Placebo, SC injection,	Phase 4 # treatment arms, 2 # centres, 21 Randomisation, 1:1 Blinding: Double	Naïve	82	12	BASDAI CFB @ Week 12	Dougados 2011[98]
Tofacitinib Phase 3 Study (NCT03502616)	Tofacitnib 5 mg, twice daily, oral tablets	Placebo, twice daily, oral tablets,	Phase 3 # treatment arms, 2 # centres, 75 Randomisation, 1:1 Blinding: Double	Mixed (approximately 20% of patients IR to ≤2 TNFi or have prior bDMARD use without IR) Data for naïve and IR subgroups available	270	16	ASAS20 @ Week 16	Deodhar 2021 [99]

Study	Intervention arm(s)	Comparator arm(s)	Study design	bDMARD experience	Total N	Duration of randomized phase (weeks)	Primary endpoint	Primary (secondary) reference(s) used
van Der Heijde 2006 (NCT00418548)	Etanercept, 50 mg QW or 25 mg BIW, SC injections	Placebo, BIW, SC injections	Phase 3 # treatment arms, 3 # centres, 38 Randomisation, 3:3:1 Blinding: Double	Mixed (patients previously treated with bDMARDs less than 4 weeks before baseline were not eligible)	356	12	ASAS20 @ Week 12	van der Heijde 2006[100] (Braun 2007[101])

*Assumption confirmed after consultation with clinical experts.
**Number of sites for both trial populations.
bDMARD: biologic DMARD; DMARD=disease-modifying antirheumatic drug; NSAID: nonsteroidal anti-inflammatory drug; csDMARD: conventional synthetic DMARD; IV: intravenous; SSZ: sulfasalazine; CS: corticosteroids; TNF: tumor necrosis factor; INF: infliximab; ASAS: Assessment of SpondyloArthritis international Society; SC: subcutaneous; IR: inadequate response and/or intolerance; HCL: hydroxychloroquine; MTX: methotrexate; Q4W: every 4 weeks; NR: not reported; Q2W: every 2 weeks; BIW: twice weekly; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; CFB: change from baseline; ASDAS: Ankylosing Spondylitis Disease Activity Score.

Only studies that reported useful relative efficacy estimates for the relevant comparators were considered for inclusion in the NMA. For secukinumab (SEC), doses were combined by their maintenance dosage (150/300 mg) and whether there was a loading dose (LD) as SEC 150 mg was tested with and without a LD. The unlicensed 75 mg dose for SEC was excluded. Note, that although included in the treatment networks, ixekizumab 80 mg every two weeks (IXE80Q2W) is not recommended by NICE. Moreover, ixekizumab is only recommended by NICE of use in biologic experienced patients. For certolizumab pegol (CZP) and etanercept (ETN), licensed doses were considered on a monthly basis. As such, the 200 mg Q2W and 400 mg Q4W doses of CZP were combined and treated as a single treatment node in the NMA, in line with previous NICE technology appraisal TA407.[6] Likewise, for ETN, the 25 mg BIW and 50 mg QW doses were combined and treated as a single treatment node in the NMA. For the remaining interventions, different doses for an intervention were treated as separate treatment nodes in the NMA.

Outcomes considered relevant for inclusion within the submission were the primary endpoint from the SELECT-AXIS1 and SELECT-AXIS2 trials, ASAS40, and the key clinical endpoints recommended by the BSR guidelines for to assess AS activity: BASDAI50, BASDAI CFB and BASFI CFB[68] reported at a timepoint between week 12-16 (inclusive).

The NMAs pooled week 12-16 timepoints, which reflects the recommended timepoint to assess treatment response.[2,29] Therefore, for a given outcome the inputs into the NMA may have differed between interventions in terms of the timepoint considered. However, use of trial primary endpoints was considered to be the most robust approach to estimating true relative treatment effects. Data are available considering both week 12 and week 14 (primary endpoint) from the SELECT-AXIS1 and 2 trials, with the week 14 analysis presented below and the alternative week 12 analyses in Appendix D, Sections 7.3-7.5.

Studies were assessed for NMA inclusion regardless of prior biologic experience. However, separate analyses were conducted for bDMARD-naïve and bDMARD-IR patients. Several of the RCTs were conducted in populations with mixed bDMARD experience without reporting outcomes in the subgroup of interest or did not report bDMARD experience in their patient population.[69,71,73,84,95]

Only two trials were identified that included only bDMARD-IR patients.[80,97] While the MEASURE 1-5 trials[43,63,92,93] for secukinumab enrolled a mixed population, very few bDMARD-IR patients were enrolled. As these patient numbers are relatively small, the comparison cannot be considered robust and is highly likely to result in large confidence intervals. This

was highlighted in the secukinumab NICE appraisal (TA407), by the company when asked to provide further explanation on the treatment effect present in their subgroup analysis. The company stated that MEASURE1 and 2 were not powered to detect a difference between the TNFi-naïve and TNFi-experienced subgroups, and that due to the relatively small patient numbers in the TNFi-experienced subgroup, these results should not be relied on.[6] Further, eligibility criteria stipulated that patients could have received a maximum of one prior TNFi for inclusion into the MEASURE studies, which does not align with eligibility criteria within SELECT-AXIS2. Similarly, patients in the MEASURE trials were required to have a washout period after prior bDMARD experience, which again does not align with the treatment history of patients within SELECT-AXIS2. The MEASURE1 and 3 studies included IV infusions of secukinumab, which is not a licensed form of its administration, and loading doses which are also not included in the recommended administration, and so the results from these trials are not considered relevant comparators. Hence, the bDMARD-IR NMA focuses on the comparison with ixekizumab, which should be used to inform decision-making for the biologic experienced population> It is not expected that the comparison between upadacitinib and secukinumab would differ between the bDMARD-naïve and bDMARD-IR populations, and so, a scenario analysis is provided (Appendix D, Sections 7.2 and 7.5) that includes the secukinumab bDMARD-IR data.

B.3.9.1.2 NMA networks

A summary of the relevant trials and the treatment and dosing schedules considered and a summary of the endpoints of interest available for inclusion in the NMAs is provided in Appendix D, Section 5.3.

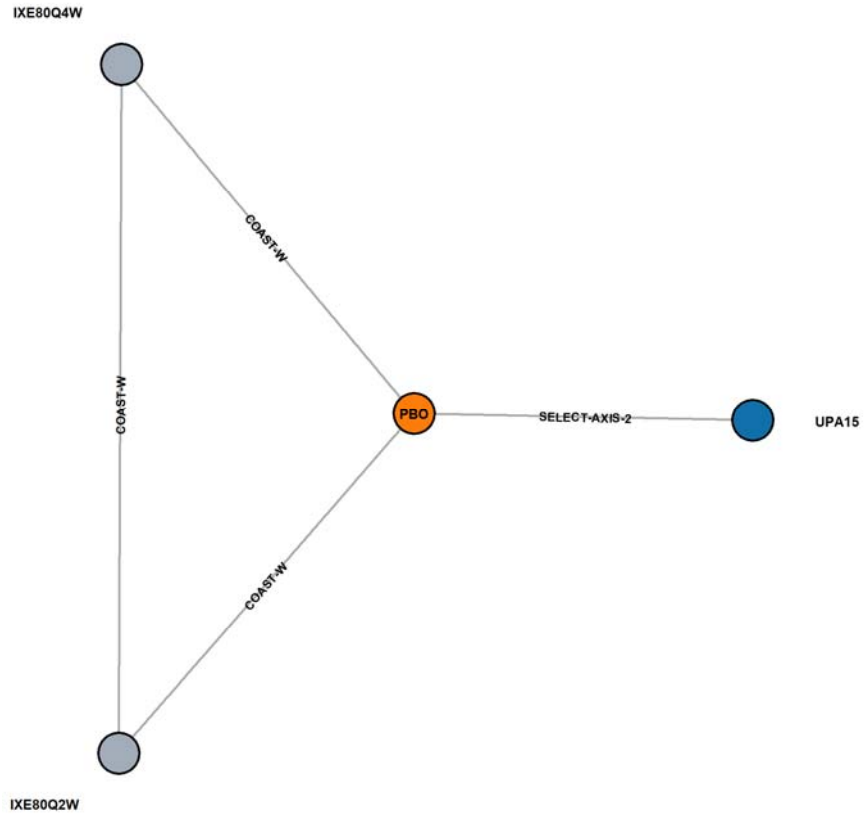
The complete treatment network of all the RCTs included in the NMAs is included in the network diagram shown in Figure 7, representing all available treatments for active AS at the time of analysis based on the criteria described in Section B.3.9.1.3. In addition, the limited treatment network for bDMARD-IR is presented in Figure 8.

Each node represents a treatment regimen included in the network and lines represent direct comparisons between nodes. The studies contributing to each comparison are also detailed along each line in the network diagram. The network diagrams considering each outcome are presented in Appendix D, Sub-appendix C.

Figure 7. Complete treatment network of RCTs among AS patients – bio-naïve network

ADA40: adalimumab 40 mg; CZP200/400: certolizumab pegol 200/400 mg; ETN50/25: etanercept 50/25 mg; GOL100/50: golimumab 100/50 mg; INF5: infliximab; IXE80Q4W/Q2W: ixekizumab 80 mg every 4 weeks/every 2 weeks; PBO: placebo; SEC150/300 (no LD): secukinumab 150/300 mg (no loading dose); TOF2/5/10: tofacitinib: 2/5/10 mg; UPA15: upadacitinib 15 mg

Figure 8. Limited treatment network of RCTs among bDMARD-IR patients



IXE80Q4W/Q2W: ixekizumab 80 mg every 4 weeks/every 2 weeks; PBO: placebo; UPA15: upadacitinib 15 mg

B.3.9.1.3 Methods and outcomes of included studies

NMAs were conducted to compare the relative efficacy off upadacitinib with relevant clinical comparators in bDMARD-naïve and bDMARD-IR patients at 12 to 16 weeks of treatment.

Population

The relevant studies identified included patients with active AS, defined as BASDAI ≥4, at baseline, see Appendix C for further detail of the PICOS criteria. Most RCTs further imposed minimum requirements on back or spinal pain score and/or morning stiffness. All included RCTs randomised patients to an active treatment compared to a placebo arm for at least 12 weeks in a double-blinded manner.

Relevant demographic and baseline characteristics were considered and reviewed across the identified trials. Baseline characteristics are presented in Appendix D, Section 5.2. Potential

sources of heterogeneity across the RCTs and baseline placebo risks are described in Section B.3.9.3 and Appendix D, Section 5.2.2.

Timepoint

Outcomes were assessed at pooled Week 12 to 16 timepoints, with a preference for timepoints closest to Week 12. The resulting timepoint used was the primary timepoint of all included RCTs except for the ASSERT study of infliximab, for which the primary timepoint was Week 24,[102] however, a 12-week timepoint was also reported.[66] For SELECT-AXIS1 and 2, both the primary timepoint (Week 14, presented in Section B.3.9.2) and the 12-week timepoint (presented in Appendix D, Sections 7.3-7.5) were considered in the NMAs.

Missing data

Included RCTs employed different strategies to impute missing outcomes as reported in Appendix D, Section 5.2.2. There appears to be a shift in imputation strategy from older to newer trials. For binary outcomes, older TNFi trials employed a mix of the conservative non-responder imputation (NRI) and last observation carried forward (LOCF) strategies, while the more recent trials for IL-17 and JAK inhibitors, all employed NRI. For continuous outcomes, older TNFi trials mostly employed LOCF, while more recent IL-17 and JAK inhibitor trials all employed a mixed-effect model of repeated measures (MMRM) to impute missing scores.

There was little to no variety in the imputation method used along each edge, thus not allowing for analytical adjustments to account for this source of heterogeneity. Therefore, it should be acknowledged that indirect comparisons involving edges with different imputation methods are potentially biased. Given that NRI is a more conservative approach than LOCF, efficacy estimates for IL-17 and JAK inhibitors are potentially reduced relative to TNFis.

B.3.9.1.4 Methods of analysis and presentation of results

For each feasible network, NMAs were conducted in a Generalized 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).[103-105] 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.[106]

A Bayesian NMA requires a likelihood distribution that reflects the nature of the data and the sampling process that generated them, and a transformation (link function) that maps the data

into a continuous measure between plus and minus infinity. 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.[103,104]

By default, trial-specific baselines μ were modelled as independent, such that an unrelated model parameter was specified for each one. However, in models with sparse data, exchangeable μ's with random effects were considered to help with parameter estimation.[104]

For all networks, both fixed effects (FE) and random effects (RE) models were tested. Per the NICE DSU TSD2, each model's global fit was assessed and compared using their overall residual deviance (Dbar), effective number of parameters (pD), deviance information criteria (DIC), leverage plots and the posterior distribution of the between-study standard deviation (SD) associated with the RE model.[103,104]

As presented in Appendix D, sub-appendix G, for each preferred model, a baseline risk-adjusted version was conducted that adjusted for differences in mean placebo effect across studies, using the code provided in NICE DSU Technical Support Document 3 (TSD3).[107] This adjustment captures many characteristics that are thought to modify the treatment effect, including those unmeasured or unknown, within a single measure. A common regression term B was assumed for all adjustments. The model with the baseline risk covariate was preferred if, because of its inclusion, the median posterior SD (for RE models) decreased and the 95% credible interval (CrI) of the regression term B excluded zero.[104]

As described in NICE DSU TSD2, vague or flat prior distributions were given to the parameters to be estimated by default.[103,104] For parameters assumed to be specified on a continuous scale, namely the relative treatment effects d, trial-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 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, likely when the number of units contributing to its estimation is small, or model convergence could not be achieved, a gamma (0.001, 0.001) prior distribution was tested using precision that gives a low prior weight to unfeasibly large SDs on the logit scale.[104,108]

Model Output

In the NMAs, relative treatment effects were modelled as log odds for binary outcomes and mean differences for continuous outcomes. 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 (such as the probabilities for binary and CFBs for continuous outcomes) were also predicted.[103] All posterior distributions were summarized by their medians and 95% CrIs.

B.3.9.1.5 Risk of bias

Quality assessments of each trial included in the NMA were performed according to NICE guidelines. The results of this quality assessment are shown in Appendix C.

B.3.9.2 Results

Results from the two NMA of particular relevance to the decision problem (in bDMARD-naïve and bDMARD-IR patients respectively) demonstrated no significant differences between upadacitinib and all comparators across ASAS40, BASDAI50, BASDAI CFB and BASFI CFB. These findings are further supported by a comprehensive, robust and wide range of additional analyses which presented results using alternative time trial time points, random or fixed effects models, adjusted or unadjusted NMA, and additional variables, further detailed in Appendix D, Sub-appendix G. Overall, upadacitinib has a comparable efficacy to all comparators assessed for the treatment of active AS.

B.3.9.2.1 ASAS40

For ASAS40, the primary outcome of the SELECT-AXIS trials, upadacitinib was found to be comparable to all comparators, for both RE with placebo adjustment, the preferred model, and RE without adjustment for the bDMARD-naïve population. RE model is a better fit for the data, based on a Dbar that is much closer to the number of data points (33 versus 38, compared to 33 data points), slight decrease in DIC (64 to 63), and a leverage plot with no outliers. The baseline-risk adjustment is selected because of lower median sd and significant baseline adjustment regression term.

Upadacitinib was also found to be statistically equivalent to ixekizumab in the preferred FE model for the bDMARD-IR population. The IR dataset was deemed too sparse to inform the RE model, the FEA model did not converge, subsequently the FE model was selected. Of note, with the exception of no sd estimation, the fit of the FE model was similar to that of RE.

See Appendix D, Section 5.3 for more detail on model selection for both the bDMARD-naïve and -IR populations.

The results for relative comparisons of upadacitinib versus comparators for the ASAS40 binary outcome are summarised in Table 24. Note: results for the RE and REA models are included in Appendix D, Sections 7.1-7.5 for completeness.

B.3.9.2.2 BASDAI50

For BASDAI50, a key indicator of treatment response in AS, upadacitinib was found to be comparable to all comparators, both RE with placebo adjustment and without adjustment, the preferred RE model, for the bDMARD-naïve population. Going from FE to RE models, there was a slight improvement in model fit: Dbar decreased by more than 1 point to be closer to the number of data points, though with an insignificant increase in DIC (43.5 to 44.5). As such, the RE model is selected. Baseline-risk adjustment of the RE model appears to be unnecessary as it is associated with an insignificant B (-0.64 [95% CrI: -2.78 to 1.56]).

Upadacitinib was also found to be comparable to ixekizumab in the preferred FE model for the bDMARD-IR population. The IR dataset was deemed too sparse to inform the RE model, the FEA model did not converge, subsequently the FE model was selected. Of note, with the exception of no sd estimation, the fit of the FE model was similar to that of RE. See Appendix D, Section 5.3 for more detail on model selection for both the bDMARD-naïve and bDMARD -IR populations.

The results for relative comparisons of upadacitinib versus comparators for the BASDAI50 binary outcome are summarised in Table 25. Note: results for the RE and REA models are included in Appendix D, Sections 7.1-7.5 for completeness.

Table 24. Odds ratios of ASAS40 for upadacitinib versus comparators – Week 14

	Median	Lower 95% CrI	Upper 95% CrI	Median	Lower 95% CrI	Upper 95% CrI
bDMARD-naïve population	**RE (unadjusted)**			**REA***		
UPA15						
ADA40						
CZP200/400						
ETN25/50						
GOL100						
GOL50						
INF5						
IXE80Q2W						
IXE80Q4W						
SEC150						
bDMARD-IR population	**FE (unadjusted)***			**FEA**		
Placebo						
UPA15						
IXE80Q2W						
IXE80Q4W						

* Preferred model; **Indicates a statistically significant result.
Treatments: ADA40: adalimumab 40 mg; CZP200/400: certolizumab pegol 200/400 mg; ETN50/25: etanercept 50/25 mg; GOL100/50: golimumab 100/50 mg; INF5: infliximab; IXE80Q4W/Q2W: ixekizumab 80 mg every 4 weeks/every 2 weeks; PBO: placebo; SEC150/300 (no LD): secukinumab 150/300 mg (no loading dose); TOF2/5/10: tofacitinib: 2/5/10 mg; UPA15: upadacitinib 15 mg,
bDMARD: biologic disease modifying antirheumatic drug; CrI: credible interval; FE: fixed effects model; FEA: placebo adjusted fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; RE: random effects model; REA: placebo adjusted random effects model;

Table 25. Odds ratios of BASDAI50 for upadacitinib versus comparators – Week 14

	Median	Lower 95% CrI	Upper 95% CrI	Median	Lower 95% CrI	Upper 95% CrI
bDMARD-naïve population	**RE (unadjusted)***			**REA**		
UPA15						
ADA40						
CZP200/400						
ETN25/50						
GOL100						
GOL50						
INF5						
IXE80Q2W						
IXE80Q4W						
SEC150						
bDMARD-IR population	**FE (unadjusted)***			**FEA**		
Placebo						
UPA15						
IXE80Q2W						
IXE80Q4W						

* Preferred model; **Indicates a statistically significant result.
Treatments: ADA40: adalimumab 40 mg; CZP200/400: certolizumab pegol 200/400 mg; ETN50/25: etanercept 50/25 mg; GOL100/50: golimumab 100/50 mg; INF5: infliximab; IXE80Q4W/Q2W: ixekizumab 80 mg every 4 weeks/every 2 weeks; PBO: placebo; SEC150/300 (no LD): secukinumab 150/300 mg (no loading dose); TOF2/5/10: tofacitinib: 2/5/10 mg; UPA15: upadacitinib 15 mg,
bDMARD: biologic disease modifying antirheumatic drug; CrI: credible interval; FE: fixed effects model; FEA: placebo adjusted fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; RE: random effects model; REA: placebo adjusted random effects model;

B.3.9.2.3 BASDAI CFB

The BASDAI CFB indicates the change in patients' disease activity during treatment from baseline. For BASDAI CFB, upadacitinib was found to be comparable to all comparators, both with placebo adjustment, the preferred RE model, and RE without adjustment for the bDMARD-naïve population. The RE model is a better fit than the FE model: Dbar decreased from 48 to 37 compared to 37 data points and all points in the leverage plot fell within the c=3 line. The DIC also fell by ~5 points, making the RE model more parsimonious. The baseline-risk adjustment of the RE model is selected since the median sd fell from 0.38 to 0.09 and the baseline-risk adjustment factor is significant (-0.93 [95% CrI: -1.31 to -0.56]).

Upadacitinib was also found to be comparable to ixekizumab in the preferred FE model for the bDMARD-IR population. The IR dataset was deemed too sparse to inform the RE model, subsequently the FE model was selected. Of note, with the exception of no sd estimation, the fit of the FE model was similar to that of RE. See Appendix D, Section 5.3 for more detail on model selection for both the bDMARD-naïve and -IR populations.

The results for relative comparisons of upadacitinib versus comparators for the BASDAI CFB continuous outcome are summarised in Table 26. Note: results for the RE and REA models are included in Appendix D, Sections 7.1-7.5 for completeness.

Table 26. Relative effect of BASDAI CFB for upadacitinib versus comparators – Week 14

	Median	Lower 95% CrI	Upper 95% CrI	Median	Lower 95% CrI	Upper 95% CrI
bDMARD-naïve population	**RE (unadjusted)**			**REA***		
UPA15						
ADA40						
CZP200/400						
ETN25/50						
GOL100						
GOL50						
INF5						
IXE80Q2W						
IXE80Q4W						
SEC150						
bDMARD-IR population	**FE (unadjusted)***			**FEA**		
Placebo						
UPA15						
IXE80Q2W						
IXE80Q4W						

* Preferred model; **Indicates a statistically significant result.
Treatments: ADA40: adalimumab 40 mg; CZP200/400: certolizumab pegol 200/400 mg; ETN50/25: etanercept 50/25 mg; GOL100/50: golimumab 100/50 mg; INF5: infliximab; IXE80Q4W/Q2W: ixekizumab 80 mg every 4 weeks/every 2 weeks; PBO: placebo; SEC150/300 (no LD): secukinumab 150/300 mg (no loading dose); TOF2/5/10: tofacitinib: 2/5/10 mg; UPA15: upadacitinib 15 mg,
bDMARD: biologic disease modifying antirheumatic drug; CrI: credible interval; FE: fixed effects model; FEA: placebo adjusted fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; RE: random effects model; REA: placebo adjusted random effects model;

B.3.9.2.4 BASFI CFB

BASFI is an indicator of a patient's pain and stiffness, which are the most common symptoms of AS. For BASFI CFB, upadacitinib was found to be comparable to all comparators, for both FE with and without placebo-adjustment, the preferred FE model, for the bDMARD-naïve population. Model fit statistics, presented in Appendix D Section 5.3, show there to be very little cross-study heterogeneity and thus, little gain in fit from the RE model (i.e., no meaningful differences in Dbar and leverage plots). Thus, the more parsimonious FE model is selected. The baseline-risk adjustment appears to be unnecessary given an insignificant B (-0.56 [95% CrI: -1.3 to 0.33]).

Upadacitinib was also found to be comparable to ixekizumab in the preferred FE model for the bDMARD-IR population. The IR dataset was deemed too sparse to inform the RE model, the FEA model did not converge, subsequently the FE model was selected. Of note, with the exception of no sd estimation, the fit of the FE model was similar to that of RE. See Appendix D, Section 5.3 for more detail on model selection for both the bDMARD-naïve and -IR populations.

The results for relative comparisons of upadacitinib versus comparators for the BASDAI CFB continuous outcome are summarised in Table 27Table 27. Note: results for the RE and REA models are included in Appendix D, Sections 7.1-7.5 for completeness.

Table 27. Relative effect of BASFI CFB for upadacitinib versus comparators – Week 14

	Median	Lower 95% CrI	Upper 95% CrI	Median	Lower 95% CrI	Upper 95% CrI
bDMARD-naïve population	**FE (unadjusted)***			**FEA**		
UPA15						
ADA40						
CZP200/400						
ETN25/50						
GOL100						
GOL50						
INF5						
IXE80Q2W						
IXE80Q4W						
SEC150						
bDMARD-IR population	**FE (unadjusted)***			**FEA**		
Placebo						
UPA15						
IXE80Q2W						
IXE80Q4W						

* Preferred model; **Indicates a statistically significant result.
Treatments: ADA40: adalimumab 40 mg; CZP200/400: certolizumab pegol 200/400 mg; ETN50/25: etanercept 50/25 mg; GOL100/50: golimumab 100/50 mg; INF5: infliximab; IXE80Q4W/Q2W: ixekizumab 80 mg every 4 weeks/every 2 weeks; PBO: placebo; SEC150/300 (no LD): secukinumab 150/300 mg (no loading dose); TOF2/5/10: tofacitinib: 2/5/10 mg; UPA15: upadacitinib 15 mg,
bDMARD: biologic disease modifying antirheumatic drug; CrI: credible interval; FE: fixed effects model; FEA: placebo adjusted fixed effects model; NA: not applicable (i.e., could not be included in network); OR: odds ratio; RE: random effects model; REA: placebo adjusted random effects model;

B.3.9.3 Results of the assessment of heterogeneity

Relevant study and patient characteristics were considered and reviewed across the included RCTs to get a sense of their comparability and identify potential sources of cross-study heterogeneity. The following baseline characteristics were identified a priori from published clinical research[109-112] to be potential treatment effect modifiers: age, duration of disease, CRP levels (mg/L), human leukocyte antigen B27 (HLA-B27) status (positive versus negative), functional status (BASFI scores), disease severity (BASDAI scores), and Total Back Pain scores

There appears to be minimal cross-study heterogeneity with respect to baseline patient characteristics in the networks. In summary, a small subset of the studies, four RCTs (Bao 2014[72], Hu 2012[84], Huang 2014[85], MEASURE 5[93]), stood out as having younger patients than the other studies, with ages ranging from 27 to 35 years, see Appendix D (Figures 32 and 33) for detail. Since published literature suggests ≤40 years to be a predictor of response, there may be some heterogeneity with respect to age in these studies versus the other RCTs.[109,111] In addition, The SPINE study[98] had a longer duration of symptoms (approximately 20 years) than others among bDMARD-naïve RCTs (12 years on average), but otherwise, the studies appear comparable in their duration of disease.

The mean baseline (PBO) effects across the included RCTs were also assessed. To address any discernible heterogeneity across RCTs, rather than adjusting for individual characteristics, baseline risk was adjusted as a proxy for both measured and unmeasured patient- and study-level characteristics that can collectively influence a patient's response to treatment.[113-117] Overall, baseline risks for ASAS40, BASDAI50, BASDAI CFB, and BASFI CFB varied widely across the included studies, supporting the testing of each selected model with baseline risk adjustment, see Appendix D, Section 5.2.2.6 for detail.

Baseline-risk adjustment was conducted that adjusted for differences in mean placebo effect across studies using the code provided in NICE DSU Technical Support Document 3 (TSD3).[107] This adjustment captures many characteristics that are thought to modify the treatment effect, including those that were not measured or unknown, within a single measure. A common regression term B was assumed for all adjustments: the relationship between the placebo response and the active treatment response was assumed not to depend on treatment. The model with the baseline risk covariate was preferred if, because of its inclusion, the median posterior SD (for RE models), decreased and the 95% credible interval (CrI) of the

regression term B excluded zero.[104] This baseline-risk adjustment approach is commonly applied to account for heterogeneity and is consistent with previous appraisals for AS.[2,6,7]

B.3.9.4 Uncertainties in the indirect and mixed treatment comparisons

A general limitation of the NMA is that the assumptions underlying it, network connectivity, homogeneity and transitivity or consistency, must be carefully considered, because if any of them is violated, the conclusions of the NMA may be jeopardized.

To assess inconsistency in the networks, FE and RE unrelated mean (relative) effects (UME) or inconsistency models were developed and their fit (leverage plots, Dbar and DIC statistics) to corresponding consistency models was compared, as described NICE DSU Technical Support Document 4 (TSD4).[118] Plots of the individual data points posterior mean deviance contribution in each of the two models along with the line of equality were produced, see Appendix D, Section 5.3 for detail of model selection. Where inconsistency or deviation from the equality line was detected, a thorough review of the entire evidence base was conducted to identify if any trials were "different", as recommended in NICE DSU TSD4.[118]

For most networks, the heterogeneity estimates (sd), the posterior means of the residual deviance (Dbar) and the DICs are very similar between the NMA and UME models, suggesting lack of evidence for inconsistency in these networks. This is supported by the corresponding plots of individual data points' posterior mean deviance contributions for the NMA and UME models, where all points fall on the line of equality. See Appendix D, Section 5.5 for detail.

In the network diagram for primary bDMARD-IR network 4 (Figure 8), there are no loops of evidence present in the network (the loop of IXE doses is informed by the same trial on all edge and is thus not considered as 'loop' in relation to inconsistency). As such, consistency between direct and indirect evidence cannot be assessed using a node-split approach.

In the presented analysis, model fit was robustly analysed. Results presented within this analysis were drawn from models that met convergence criteria and displayed successful updating of the naïve prior distribution assumptions in the posterior distributions. There was little evidence of inconsistency in the networks analysed. Furthermore, to account for potential differences in the baseline (placebo) risk across trials, baseline risk-adjusted models were considered.

B.3.9.5 Conclusions of the ITC

During an advisory board, UK clinicians indicated that upadacitinib would be considered as an alternative therapeutic option to IL-17A inhibitors.[4] The results from the bDMARD-naïve and

bDMARD-IR NMA for both week 14 and week 12 (Appendix D, Sections 7.1-7.5) revealed no significant differences between upadacitinib and IL-17A inhibitors across ASAS40, BASDAI50, BASDAI CFB and BASFI CFB, demonstrating comparable treatment effects across all variables of interest. These findings are further supported by a comprehensive, robust and wide range of additional analyses which presented results using alternative time trial time points, random or fixed effects models, adjusted or unadjusted NMA, and additional variables (Appendix D, Sections 7.1-7.5). Overall, upadacitinib has a comparable efficacy to all TNFi and IL-17A inhibitors assessed for the treatment of active AS. Therefore, as upadacitinib was demonstrated to have comparable clinical efficacy to ixekizumab and secukinumab, it fulfils the NICE criteria for a fast-track appraisal using a cost-comparison approach (Section B.1).

B.3.10 Adverse reactions

All currently available advanced treatments for active AS are associated with adverse events. Long-term NSAID treatment is associated with hypertension, abdominal pain and cardiovascular and renal related side effects,[22-24] whilst bDMARDs are associated with multiple adverse events (AEs) including viral upper respiratory tract infection, diarrhoea and headache.[2] Similarly, corticosteroids are also associated with a number of AEs, resulting in their long-term use not being recommended for the treatment of AS. These AEs are relatively rare and are often non-serious. Upadacitinib was well-tolerated during the SELECT-AXIS1 and 2 trials, with a similar proportion of patients reporting AEs or treatment-related AEs in both the upadacitinib and placebo treatment arms.

The safety profile of upadacitinib is similar to that observed with TNFi and IL-17A inhibitors for the treatment of AS.[2,63,78,88] The proportion of patients treated with upadacitinib reporting AEs during SELECT-AXIS1 and 2 were 62% and 41%, respectively, which decreased to 1% and 3%, respectively, when considering serious AEs. During trials for ixekizumab (COAST V)[77] and secukinumab (MEASURE 1),[43] 42% and 68% of patients reported an AE, respectively, which decreased to 0% and 2% of patients, respectively, when considering serious AEs, which is similar to the proportion of AE and serious AEs reported during the SELECT-AXIS1 and SELECT-AXIS2 trials for upadacitinib.

B.3.10.1 SELECT-AXIS1

During SELECT-AXIS1, upadacitinib was generally well-tolerated, with a similar proportion of patients reporting an AE or treatment-related AE between the treatment groups. No serious infections, renal dysfunction, adjudicated major adverse cardiovascular events, venous thromboembolic or deaths were reported during study period 1 (14 weeks) and study period 2

(104 weeks). In study period 1, a higher proportion of patients in the upadacitinib arm had adverse events of increased creatine phosphokinase, all of which were asymptomatic, and most were mild and reversible without study drug interruption. One patient in the placebo arm had symptoms (muscle pain) in the setting of elevated creatine phosphokinase and permanently discontinued the study drug. One patient in the placebo arm, who did not have a history of IBD, and no patients in the upadacitinib arm reported new onset of IBD.

The overall summary of AEs in SELECT-AXIS1 is shown in Table 28 and a breakdown of the most frequent AEs, seen in ≥5% of patients in any treatment groups, is shown in Table 29

. The overall summary of treatment-emergent adverse events observed during study period 2 is shown in Table 30.

Table 28. Overall summary of adverse events through to week 14 - SELECT-AXIS1

	Placebo (n = 94) n (%)	**Upadacitinib (n = 93) n (%)**
Any adverse event	52 (55%)	58 (62%)
Serious adverse event	1 (1%)*	1 (1%)†
Adverse event leading to discontinuation	3 (3%)‡	2 (2%)§
Any infection	26 (28%)	19 (20%)
Infection in at least two patients		
Nasopharyngitis	4	5
Rhinitis	4	0
Upper respiratory tract infection	3	0
Pharyngitis	2	0
Urinary tract infection	2	0
Viral infection	2	0
Tonsilitis	0	2
Serious infection	0	0
Opportunistic infection	0	1 (1%)**
Herpes zoster	0	0
Tuberculosis	0	0
Malignancy‡‡	0	0
Gastrointestinal perforation	0	0
Hepatic disorder††	2 (2%)	5 (5%)
Renal dysfunction	0	0
Anaemia	0	0
Neutropenia	0	1 (1%)

Lymphopenia	0	0
Venous thromboembolic events (adjudicated)	0	0
Cardiovascular events (adjudicated)	0	0
Death	0	0

* Cardiovascular disorder reported as mild circulation dysregulation

† Spinal osteoarthritis, reported as moderate worsening of cervical spondylitis

‡ Dyspepsia (n=1), blood creatine phosphokinase increased (n=1) and atlantoaxial instability (n=1)

§ Otis media (n=1) and myalgia (n=1)

** Oesophageal candidiasis in patient with gastro-oesophageal reflux disease, study drug continued after treatment with fluconazole

‡‡ Including non-melanoma skin cancer, malignancy other than non-melanoma skin cancer and lymphoma

†† All seven hepatic disorders were based on asymptomatic alanine aminotransferase or aspartate aminotransferase increases and none led to premature discontinuation of study drug

Source: van der Heijde (2019)[44]

Table 29. Adverse events in ≥5% of patients in any treatment group through to week 14

	Placebo (n = 94) n (%)	**Upadacitinib (n = 93) n (%)**
Increased creatine phosphokinase*	2 (2%)	8 (9%)
Diarrhoea	5 (5%)	5 (5%)
Nasopharyngitis	4 (4%)	5 (5%)
Headache	2 (2%)	5 (5%)
Nausea	5 (5%)	1 (1%)

* All asymptomatic except for one patient in the placebo group

Source: van der Heijde (2019)[44]

Table 30. Treatment-emergent adverse events at the end of study period 2 (week 104)

AE, E (E/100 PY)	**Upadacitinib (n = 182) (237.6 PY) n (%)**
Any adverse event	618 (260.1)
Serious adverse event	14 (5.9)
Adverse event leading to discontinuation	15 (6.3)
Any infection	205 (86.3)
Serious infection	0
Opportunistic infection	2 (0.8)
Herpes zoster	5 (2.1)
Active tuberculosis	0
Creatinine phosphokinase elevation	28 (11.8)

Hepatic disorder	24 (10.1)
Neutropenia	7 (2.9)
Anaemia	3 (1.3)
Lymphopenia	2 (0.8)
Renal dysfunction	0
Gastrointestinal perforation	0
Malignancy	1 (0.4)
Adjudicated MACE	0
Adjudicated VTE	0
Uveitis	13 (5.5)
Inflammatory bowel disease	0
Death	0
MACE: major adverse cardiac events; PY: patient years; VTE: venous thromboembolism; Source: Deodhar et al. 2021[119]	

B.3.10.2 SELECT-AXIS2

The overall summary of treatment-emergent adverse events (TEAEs) and treatment-emergent adverse events of special interest (AESI) in SELECT-AXIS2 is shown in Table 31 and Table 32.

The rate of overall AEs was similar between the upadacitinib and placebo arms. Serious AEs were reported more frequently with upadacitinib ([redacted]%] compared to [redacted]%]), the majority of which were COVID-19 or COVID-19 pneumonia. For AEs leading to discontinuation, none were reported in the upadacitinib arm compared to [redacted] ([redacted]%) in the placebo arm. No deaths were reported.

Serious infections and herpes zoster were reported in the upadacitinib arm ([redacted]% and [redacted]%, respectively compared to 0 in the placebo arm). Four of the five serious infections were COVID-19 or COVID-19 pneumonia. Neither herpes zoster events were serious, did not lead to treatment discontinuation, and involved a single dermatome. All hepatic disorders reported in the upadacitinib group were mild or moderate transaminase elevations; none were serious or led to discontinuation of treatment. There were no events of opportunistic infection, non-melanoma skin cancer, lymphoma, adjudicated GI perforation, renal dysfunction, active tuberculosis, adjudicated MACE or VTE reported.

Table 31. Overview of treatment-emergent adverse events up to week 14 - SELECT-AXIS2

	Placebo (n = 209) n (%)	Upadacitinib (n = 211) n (%)
Adverse event (AE)	[redacted]	[redacted]
AE with reasonable possibility of being related to study treatment*	[redacted]	[redacted]
Severe AE	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]
AE leading to withdrawal of study treatment	[redacted]	[redacted]
AE leading to death	[redacted]	[redacted]
COVID-19 related AE†	[redacted]	[redacted]
All deaths	[redacted]	[redacted]

* As assessed by investigator

† As collected in AE eCRF

Source: SELECT-AXIS2 CSR[65]

Table 32. Overview of treatment-emergent adverse events of special interest up to week 14 - SELECT-AXIS2

	Placebo (n = 209) n (%)	Upadacitinib (n = 211) n (%)
Infection	[redacted]	[redacted]
Serious infection	[redacted]	[redacted]
Opportunistic infection excluding tuberculosis and herpes zoster	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
Active tuberculosis	[redacted]	[redacted]
Malignancy	[redacted]	[redacted]
Non-melanoma skin cancer (NMSC)	[redacted]	[redacted]
Malignancy other than NMSC	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]
Hepatic disorder	[redacted]	[redacted]
Adjudicated gastrointestinal perforation	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]
Adjudicated MACE*	[redacted]	[redacted]
Adjudicated VTE**	[redacted]	[redacted]

* MACE; Major adverse cardiovascular events, defined as cardiovascular death (includes acute myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedure-related death, death due to cardiovascular haemorrhage, fatal stroke, pulmonary embolism and other cardiovascular causes), non-fatal myocardial infarction and non-fatal stroke.

** VTE include deep vein thrombosis (DVT) and pulmonary embolism (PE) (fatal and non-fatal).

Source: SELECT-AXIS2 CSR [65]

B.3.11 Conclusions about comparable health benefits and safety

Upadacitinib is a first-in-class, oral JAK inhibitor for the treatment of active AS in adults who have responded inadequately to conventional therapy. The targeting of JAK represents a novel mechanism of action that offers patients and healthcare providers an alternative to IL-17A inhibitors, especially in patients who have responded inadequately or cannot tolerate these treatments or where these treatments are not recommended, such as in patients with IBD.[5] Upadacitinib is also the first oral therapy available for patients with active AS, offering patients a more convenient mode of administration and providing relief for patients with needle-phobia.

The clinical effectiveness of upadacitinib 15 mg QD was demonstrated in two international, multicentre, placebo-controlled Phase II/III trials: SELECT-AXIS1 and SELECT-AXIS2. SELECT-AXIS1 included patients with active AS who had an inadequate response to or contraindication for NSAIDs. SELECT-AXIS2 study 1 included patients with active AS who had an inadequate response or intolerance to bDMARDs. Given that concomitant medications such as NSAIDs and physical therapy were permitted during the trials, the placebo arms can be considered to represent a proxy for conventional care in the UK.

SELECT-AXIS1 and SELECT AXIS2 were high-quality trials where the inclusion criteria selected patients with active AS, defined as a BASDAI ≥ 4 and a Patient's Assessment of Total Back Pain ≥ 4 based on a 0-10 NRS at the screening and baseline visits.[44,57] This corresponds to the definition of active AS applied in UK in current BSR guidance.[61] Therefore, the patients enrolled in both trials are considered generalisable to the UK population of patients with active AS.

Due to the slow and variable nature of the spinal progression observed in AS, it is impossible to conduct a 'gold standard' RCT in AS where structural progression is considered as the primary endpoint, as patients would need to be measured over a long a period of time (~2 years), which would not be considered ethical or practical.[120] Therefore, RCTs in AS focus on disease activity, physical functioning and QoL measures, considering spinal progression, both in the short and long-term, as a secondary endpoint. The endpoints covered in the evidence base, covering disease activity, physical function, quality of life and radiographic outcomes are highly relevant to the decision problem. The primary outcome, ASAS40, is a stringent response outcome, considered by the EMA to be an appropriate primary efficacy endpoint to assess major clinical response.[121]

Upadacitinib shows a greater treatment response compared to placebo

The efficacy of upadacitinib was demonstrated in the SELECT-AXIS1 and SELECT-AXIS2 trials (Section B.3.6.1 and Section B.3.6.2). Upadacitinib showed high efficacy throughout the SELECT-AXIS1 trial, achieving a greater treatment response at week 14 compared to the placebo arm (52% of patients in the upadacitinib arm achieved an ASAS40 response compared to 26% of patients in the placebo arm).[44] This treatment response was rapid, with a significant improvement in ASAS40 in the upadacitinib arm compared to the placebo arm observed after two weeks of treatment (16.1% of patients in the upadacitinib arm compared to 1.1% of patients in the placebo arm), and was sustained over the 14 week trial.

Secondary outcomes including ASAS20, BASDAI50 and ASQoL, assessed disease activity, physical function, disease progression and quality of life. Key secondary outcomes, such as the change from baseline in MRI SPARCC score of SI joints, ASDAS and BASDAI50 significantly improved in the upadacitinib arm compared to the placebo arm. Therefore, upadacitinib demonstrated statistically significant improvement in signs, symptoms and physical function compared to placebo.

Upadacitinib also demonstrated high efficacy during the SELECT-AXIS2 trial study 1, where significantly more patients achieved ASAS40 treatment response in the upadacitinib arm compared to the placebo arm at week 14 (44.5% vs 18.2%, respectively). Upadacitinib showed onset of effect in ASAS40 as early as week 4. A significant improvement was also seen in all ranked secondary endpoints, which were stringent measurements of disease activity (all $p<0.0001$).[65]

Comparative effectiveness: indirect comparison

During an advisory board, UK clinicians confirmed that upadacitinib would be considered as an alternative therapeutic option to IL-17A inhibitors.[4] As there is no head-to-head trial evidence directly comparing upadacitinib to secukinumab or ixekizumab, relative effectiveness was estimated by conducting Bayesian NMAs, as described in Section B.3.9.

Results from the bDMARD-naïve and bDMARD-IR NMA demonstrated no significant differences between upadacitinib and IL-17A inhibitors across ASAS40, BASDAI50, BASDAI CFB and BASFI CFB. These findings are further supported by a comprehensive, robust and wide range of additional analyses which presented results using alternative time trial time points, random or fixed effects models, adjusted or unadjusted NMA, and additional variables (Appendix D). Overall, upadacitinib has a comparable efficacy to IL-17A inhibitors assessed for the treatment of active AS.

Upadacitinib is well tolerated

All currently available advanced treatments for active AS are associated with adverse events, which tend to be non-serious.

During SELECT-AXIS1, a similar proportion of AEs were reported in the upadacitinib and placebo arms, 62% and 55% respectively.[44] Only 1 (1%) serious adverse event was reported in each arm and 2 (2%) of patients treated with upadacitinib experienced AEs leading to discontinuation.[44] Similarly, the rate of overall AEs observed during SELECT-AXIS2 was

similar between the upadacitinib and placebo arms. Serious AEs were reported more frequently with upadacitinib (6 [2.8%] compared to 1 [0.5%]), the majority of which were COVID-19 or COVID-19 pneumonia. No AEs leading to discontinuation were reported in the upadacitinib arm compared to 3 (1.4%) in the placebo arm. No deaths were reported.

The safety profile of upadacitinib is similar to that observed with all comparators for the treatment of AS (Section B.3.10).[2,63,78,88]

B.3.12 Ongoing studies

Period 2 of the SELECT-AXIS2 trial is currently ongoing. There are no other ongoing studies for upadacitinib for the treatment of active AS.

B.4. Cost-comparison analysis

As presented in Section B.3.9 using an indirect treatment comparison, upadacitinib demonstrates comparable clinical efficacy compared to IL-17A inhibitors, when considering ASAS40, BASDAI50, BASDAI CFB and BASFI CFB. It follows that, with the exception of drug acquisition and administration costs, all other resource utilisation would likely be comparable. As such, a cost-comparison analysis has been favoured in place of a cost-effectiveness analysis. The cost-comparison analysis undertaken herein estimates total costs associated with treatment and monitoring over a five-year period, with total costs estimated as a function of time on treatment.

As described in Section B.1.1, upadacitinib is an alternative treatment to secukinumab (recommended for biologic naïve and experienced patients) and ixekizumab (recommended for biologic experienced patients only). As such, the cost-comparison analysis presented herein focuses only on the comparison of cost outcomes associated with upadacitinib, secukinumab, and ixekizumab.

B.4.1 Changes in service provision and management

AS is a life-long, progressive condition that can lead to irreversible spinal deformities and a reduced QoL. There is a high unmet treatment need in AS for more treatment options offering an alternative mechanism of action and mode of administration to currently available IL-17A inhibitors.

Currently, all existing treatment options for active AS are administered via a subcutaneous injection or an intravenous infusion, initially administered in the secondary care setting. As an

oral formulation, upadacitinib offers an alternative mode of administration to patients who desire greater convenience or suffer from needle-phobia (Section B.1.3.4).

Based on the justifications described in Section B.1.1, ixekizumab and secukinumab have been identified as the key comparators of interest. As such, the cost-comparison analysis presented herein focuses only on the comparison of cost outcomes associated with upadacitinib versus ixekizumab and secukinumab. Ixekizumab and secukinumab are administered via subcutaneous injection and are therefore, associated with different administration costs compared to upadacitinib which is administered orally. However, the main resource use component associated with all treatments is the underlying drug cost. Monitoring costs for all treatments are expected to be similar, and it is anticipated that 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 undertaken herein estimates total costs associated with treatment and monitoring over a five-year period, with total costs disaggregated by individual year. Rates of discontinuation and monitoring are similar across treatments, which is supported by clinician feedback. Upfront administration costs differ to include the training required for initial subcutaneous injection treatment, however the long-term administration costs for patients with AS is considered similar for both oral and subcutaneous treatments. Therefore, any material differences in total cost are expected to be realised through the differences in drug acquisition price. Given the relatively low discontinuation rates associated with treatment and the similarity in the treatment pathways being compared, a five-year time horizon has been considered appropriate. Consistent with the cost-comparison approach adopted in TA497 (golimumab for treating non-radiographic axial spondyloarthritis),[39] cost outcomes are also compared over a one-year period. The adopted time horizon is considered more than adequate to reflect materially important differences between the technologies being compared.

Across all previous appraisals, consensus exists that the discontinuation rates for AS therapies are likely to be similar. With this in mind, final analyses undertaken by companies and external review groups have typically favoured the application of a standard discontinuation rate across all modelled therapies. Given the anticipated similarity between upadacitinib and its comparators (as demonstrated in Section **Error! Reference source not found.**), it is also expected that upadacitinib will observe a similar long-term discontinuation

rate. With this in mind, the base case analysis adopts a standard annual discontinuation probability of 11% (a 3-monthly equivalent of 2.87%) in line with assumptions preferred by external review groups in NICE TA383,[2] TA407,[6] and TA718.[7]

Discontinuation probabilities were applied at 3-monthly intervals, in line with cycle lengths used in recent NICE technology appraisals for AS (TA383[2], TA407[6] and TA719[40]). Once patients discontinue therapy it is assumed they incur no further cost for the purpose of this analysis. Whilst discontinuation rates are decidedly comparable across treatments and the base case adopts an approach considered appropriate in the most recent AS technology appraisals.

B.4.2.2 Intervention and comparator acquisition costs

Drug acquisition costs for upadacitinib and its comparators are described in Table 33, alongside details of relevant patient access schemes. All treatments are assumed to be administered at licensed dose, based on the doses cited by the BNF[41] and those administered in pivotal studies,[43,44] ensuring that costs represent clinically feasible doses. Drug acquisition costs were sourced from the BNF; no biosimilar or generic agents are available for any of the treatments evaluated.

Table 33. Acquisition costs of the intervention and comparator technologies

	Upadacitinib (Treatment)	Ixekizumab (Comparator)	Secukinumab (Comparator)
Summary of product			
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[122]	BNF[122]	BNF[122]
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	Initially 160 mg for 1 dose, then maintenance 80 mg every 4 weeks	Once every week for 5 doses, then maintenance once every month
Dose size	15mg	80mg	150mg
Units in dose	1	1	1
Number of doses in initial 3 months	91.31	4	7
Number of doses in subsequent 3-month periods (B)	91.31	3.26	3
Source	BNF[122]	BNF[122]	BNF[122]
Summary of costs per dose			
Cost per dose (£)	£28.77	£1,125.00	£609.39
Description of PAS (if relevant)	Upadacitinib is expected to be offered at an annual price of £[redacted] per person (assuming complete adherence). Assuming 365.25 doses a year, this equates to a PAS discount of [redacted]% which is applied in the base case.	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 (£) – After PAS applied	[redacted]	NA	NA

BNF: British National Formulary; PAS: patient access scheme

Notes:

A: Consistent with previous appraisals, no dose escalation to 300mg is modelled 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

As the assumption underpinning the analysis is that upadacitinib, ixekizumab and secukinumab are comparable in terms of health outcomes, it follows that, with the exception of drug acquisition and administration costs which are described above, all other resource utilisation would also be comparable. However, given small differences in discontinuation are modelled in scenario analyses, monitoring costs alongside drug costs have been included in the analysis, for completeness.

Drug administration costs are described in Table 34 and monitoring costs and their application are described in Table 35**Error! Reference source not found.**. All prices represent 2019/20 costs.

Table 34. Summary of drug administration costs

Administration type	Cost per administration	Justification / Source
First administration		
Subcutaneous	£48.00	Assumed one hour of nurse time for first administration and training. PSSRU 2020. Cost per working hour for nurses in Band 6.[48]
Oral	£0.00	Assumed no administration cost for oral treatments
Subsequent administration		
Subcutaneous	£0.00	Assumed self-administered following training on first administration
Oral	£0.00	Assumed no administration cost for oral treatments
PSSRU: Personal Social Services Research Unit		

Table 35. Summary of treatment monitoring costs

Monitoring component	Cost per component	Frequency of use (A)		Justification / Source
		Initial 3 months	Subsequent 3-month periods	
Specialist visits	£125.44	2	0.5	TA407[6]; Emery et al. (2018)[46]; Corbett et al. (2016)[47]; NHS Reference Costs 2019/20 (WF01A - Total HRG)[45]
Full blood count	£2.56	2	1	TA407[6]; Emery et al. (2018)[46]; Corbett et al. (2016)[47]; NHS Reference Costs 2019/20 (DAPS05 - Total Other Currencies)[45]
Erythrocyte sedimentation rate	£2.56	2	1	
Liver function test	£1.20	2	1	TA407[6]; Emery et al. (2018)[46]; Corbett et al. (2016)[47]; NHS Reference Costs 2019/20 (DAPS04 - Total Other Currencies)[45]
Urea and electrolytes test	£1.20	2	1	
Chest radiograph	£27.14	1	0	TA407[6]; Emery et al. (2018)[46]; Corbett et al. (2016)[47]; NHS Reference Costs 2019/20 (WF01B - CL - Diagnostic Imaging - First Attendance)[45]
Tuberculosis Heaf test (B)	£9.55	1	0	TA407[6]; Emery et al. (2018)[46]; Corbett et al. (2016)[47]; TA383[2]; PSSRU 2020[48]
Antinuclear antibodies	£7.35	1	0	TA407[6]; Emery et al. (2018)[46]; Corbett et al. (2016)[47]; NHS Reference Costs 2019/20 (DAPS06 - Total Other Currencies)[45]
DNA double-strand test	£7.35	1	0	

DNA: deoxyribonucleic acid; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.
Notes
A: Monitoring costs are applied to all patients receiving treatment, equally across treatment arms
B: Cost could not be sourced from contemporary literature and so the cost used in TA383 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 **Error! Reference source not found.**.1 and Section B.3.10.2, treatment with upadacitinib was extremely well tolerated with very few serious adverse events, and a similar adverse event profile to that of the placebo comparator arm in both SELECT-AXIS1 and SELECT-AXIS2. As such, it is not anticipated that adverse events would contribute significantly to cost outcome estimates. This is further supported by review of the TAs identified in Section **Error! Reference source not found.**, which demonstrate minimal impact of adverse events in both base case analysis and sensitivity analyses.

With the above in mind, the assumption that upadacitinib, ixekizumab and secukinumab observe consistent adverse event profiles has been made. As such, adverse event costs are not modelled as they are expected to be consistent across treatments. This approach also is consistent with the FTA approach adopted in TA497.[39]

B.4.2.5 Miscellaneous unit costs and resource use

As the assumption underpinning the analysis is that upadacitinib, ixekizumab and secukinumab are comparable in terms of health outcomes (Section B.3.9), it follows that, with the exception of drug acquisition and administration costs which are described above, all other resource utilisation, including that encompassed by 'miscellaneous unit costs and resource use', would also be comparable. As such, no additional miscellaneous unit costs or resource use components were identified or incorporated in the analysis.

B.4.2.6 Clinical expert validation

Cost components incorporated in this analysis have been identified based on their use in previous NICE submissions (TA383, TA407 and TA718[2,6,7]), the most recent of which was published in 2021. External review groups evaluating each of these appraisals, alongside NICE itself, have confirmed the appropriateness of the costing approach. The contemporary relevance of these cost components was confirmed during an advisory board consultation hosted by AbbVie in which clinical and health economic experts were consulted,[4] and the approach adopted in previous TAs was confirmed as consistent with current clinical practice. Subsequently, the latest (2019/20) cost estimates for each component have been identified and utilised.

B.4.2.7 Uncertainties in the inputs and assumptions

Some uncertainty exists with regards to the estimation of treatment discontinuation probabilities, particularly for upadacitinib beyond the first year for which data is not yet

available. The assumption underpinning the analysis is that upadacitinib, ixekizumab and secukinumab are comparable in terms of health outcomes, including between biologic-naïve and experienced populations, and so similar discontinuation rates are expected. This is supported by the comparison across upadacitinib and secukinumab studies, where discontinuation rates are consistent across the different time periods analysed. Inherently, uncertainty in discontinuation probabilities creates uncertainty in cost outcomes, however, to further address any uncertainty additional scenario analysis has been provided to assess the impact of alternative discontinuation assumptions (Section **Error! Reference source not found.**).

B.4.3 Base-case results

Results of the analyses are presented in **Error! Not a valid bookmark self-reference.**. The cost-comparison analysis demonstrates that treatment with upadacitinib is likely to result in a cost-saving approach to AS therapy when compared to ixekizumab and secukinumab. The estimated cost savings are expected to be between [redacted] and [redacted] per patient per year versus ixekizumab when using upadacitinib, and up to [redacted] over a five-year period. Similarly, the estimated cost savings are expected to be between [redacted] and [redacted] per patient per year versus secukinumab, and up to [redacted] over a five-year period.

Table 36. Base case cost comparison results

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Proportion remaining on treatment at 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	12.98	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	£15,117	£12,749	£11,346	£10,098	£8,987	£58,297
Secukinumab	£9,957	£6,473	£5,761	£5,127	£4,563	£31,881
Incremental undiscounted costs (A)						
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

B.4.4 Sensitivity and scenario analyses

Given potential uncertainty in the likelihood of treatment discontinuation, and the similarity between probabilities across treatments, four scenario analyses were undertaken. Each of the scenarios is described further in Table 37. Results of all scenario analyses are presented in **Error! Reference source not found.** to Table 41, and demonstrate the robustness of results to the choice of discontinuation assumptions.

Table 37. Overview of discontinuation scenario analyses

Scenario	Discontinuation approach	Description / justification
Scenario 1	Standard annual discontinuation probability of 6.57%	Using more recent data than that used to generate the discontinuation probability estimate of 11% used in previous appraisals, data from a UK study was used to estimate the annual probability of discontinuation for index axial spondyloarthritis treatment and second axial spondyloarthritis treatment.[123] Median drug survival estimates of 10.2 years and 5.5 years, for index and second treatment, respectively, were converted to annual probabilities using an exponential approximation [A].
Scenario 2	Standard annual discontinuation probability of 11.84%	
Scenario 3	Discontinuation probabilities derived from pivotal clinical trial data (different probabilities for each treatment)	Discontinuation data was derived from the pivotal clinical trials for upadacitinib, ixekizumab and secukinumab. The derivation of probabilities is described in **Error! Reference source not found.**.
Notes: A: Exponential approximation based on equation: Annual probability = 1-exp(ln(0.5)/[median survival time])		

Table 38. Treatment discontinuation

	Upadacitinib (Treatment)			Ixekizumab (Comparator)	Secukinumab (Comparator)					
Discontinuation (initial 3 months)										
Source	SELECT-AXIS1 – Initial period Van der Heijde et al. (2019)[44]	SELECT-AXI2 – Initial period[65]	Sum / Weighted Average	COAST-V – Initial period van der Heijde et al. (2018)[77]	MEASURE 1 – Initial period Baeten et al. (2015)[43]	MEASURE 2 – Initial period Baeten et al. (2015)[43]	MEASURE 3 – Initial period Pavelka et al. (2017)[63]	MEASURE 4 – Initial period Kivitz et al. (2018)[92]	MEASURE 5 – Initial period Huang et al. (2020)[124]	Sum / Weighted Average
Duration of observations (weeks) (A)	14	14	14	16	16	16	16	16	16	16
Total number of patients	93	211	304	81	125	72	74	116	305	692
Number discontinuing for any reason	4	5	9	3	4	6	0	2	7	19
Discontinuation probability during period (B)	4.30%	2.37%	2.96%	3.70%	3.20%	8.33%	0.00%	1.72%	2.30%	2.75%
3-month discontinuation probability (C)	-	-	**2.76%**	**3.03%**	-	-	-	-	-	**2.24%**
Discontinuation (subsequent 3-month periods: year 1)										
Source	Select-AXIS 1 – Initial period Van der Heijde et al. (2019)[44]			COAST-V – Initial period van der Heijde et al. (2018)[77]	MEASURE 1 – Initial period Baeten et al. (2015)[43]	MEASURE 2 – Initial period Baeten et al. (2015)[43]	MEASURE 3 – Initial period Pavelka et al. (2017)[63]	MEASURE 4 – Initial period Kivitz et al. (2018)[92]	MEASURE 5 – Initial period Huang et al. (2020)[124]	Sum / Average

Duration of observations (weeks) (A)	40	36	36	36	36	88	36	44.81 weeks
Total number of patients	89	78	121	66	74	114	298	673
Number discontinuing for any reason	11	6	15	5	10	20	20	70
Discontinuation probability during period (B)	12.36%	7.69%	12.40%	7.58%	13.51%	17.54%	6.71%	10.40%
3-month discontinuation probability (C)	4.21%	2.86%	-	-	-	-	-	3.15%
Discontinuation (subsequent 3-month periods: all subsequent years)								
Source	Assumed as Secukinumab		MEASURE 1 – Year 2 Braun et al. (2017)[125]	MEASURE 2 – Year 2 Marzo-Ortega et al. (2017)[126]	MEASURE 1 – Year 3-4 Braun et al. (2019)[127]			
Duration of observations (A)	-		52	52	104			69.81 weeks
Total number of patients	-		106	61	87			254
Number discontinuing for any reason	-		9	1	9			19
Discontinuation probability during period (B)	-		8.49%	1.64%	10.34%			7.48%
3-month discontinuation probability (C)	Assumed as Secukinumab		-	-	-			1.44%

Notes
A: Average durations were combined using a weighted average of durations using the total number of patients

B: The discontinuation probability during the period was calculated as the number of patients discontinuing for any reason / the total number of patients
C: The 3-month discontinuation probability was calculated using the following formula:
$P_3 = 1-\exp(\ln(1-P_p)/(D/(365.25/4/7)))$ where P_3 = 3-month discontinuation probability; P_p = discontinuation probability during the observed period; D = Duration of observations

Table 39. Cost comparison results – Scenario 1 (flat annual discontinuation probability of 6.57%)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Proportion remaining on treatment at end of year						
Upadacitinib	93.43%	87.29%	81.56%	76.20%	71.19%	-
Ixekizumab	93.43%	87.29%	81.56%	76.20%	71.19%	
Secukinumab	93.43%	87.29%	81.56%	76.20%	71.19%	-
Total number of doses per patient per year						
Upadacitinib	356.12	332.73	310.87	290.44	271.36	-
Ixekizumab	13.20	11.88	11.10	10.37	9.69	
Secukinumab	15.70	10.93	10.21	9.54	8.92	-
Total undiscounted costs (£)						
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	£15,372	£13,624	£12,729	£11,893	£11,112	£64,730
Secukinumab	£10,088	£6,917	£6,463	£6,038	£5,642	£35,149
Incremental undiscounted costs (A)						
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notes A: A negative value represents a cost-saving for upadacitinib						

Table 40. Cost comparison results – Scenario 2 (flat annual discontinuation probability of 11.84%)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Proportion remaining on treatment at end of year						
Upadacitinib	88.16%	77.72%	68.52%	60.40%	53.25%	-
Ixekizumab	88.16%	77.72%	68.52%	60.40%	53.25%	
Secukinumab	88.16%	77.72%	68.52%	60.40%	53.25%	-
Total number of doses per patient per year						
Upadacitinib	348.61	307.33	270.94	238.86	210.57	-
Ixekizumab	12.94	10.98	9.68	8.53	7.52	
Secukinumab	15.45	10.10	8.90	7.85	6.92	-
Total undiscounted costs (£)						
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	£15,068	£12,584	£11,094	£9,781	£8,622	£57,150
Secukinumab	£9,932	£6,389	£5,633	£4,966	£4,378	£31,298
Incremental undiscounted costs (A)						
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notes A: A negative value represents a cost-saving for upadacitinib						

Table 41. Cost comparison results – Scenario 3 (discontinuation probabilities derived from pivotal trials)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Proportion remaining on treatment at end of year						
Upadacitinib	85.46%	80.64%	76.09%	71.79%	67.74%	-
Ixekizumab	88.89%	83.87%	79.14%	74.67%	70.45%	
Secukinumab	88.81%	83.80%	79.07%	74.61%	70.39%	-
Total number of doses per patient per year						
Upadacitinib	344.14	305.47	288.22	271.95	256.60	-
Ixekizumab	12.98	11.35	10.71	10.10	9.53	
Secukinumab	15.47	10.43	9.84	9.29	8.76	-
Total undiscounted costs (£)						
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	£15,114	£13,010	£12,275	£11,582	£10,928	£62,909
Secukinumab	£9,944	£6,600	£6,227	£5,876	£5,544	£34,191
Incremental undiscounted costs (A)						
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notes 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

Upadacitinib has been licensed as a treatment in other indications for several years, where its efficacy and safety profile is well established. Evidence presented in this submission supports the use of upadacitinib for the treatment of AS.

Following a cost-comparison analysis versus secukinumab and ixekizumab, savings of up to [redacted] per patient per year are anticipated with the use of upadacitinib when a PAS discount is applied to upadacitinib. This is due to the lower acquisition cost of upadacitinib compared to secukinumab and ixekizumab at expected doses. There are significant advantages to the NHS in the availability of upadacitinib, where evidence suggests efficacy comparable to secukinumab and ixekizumab, with a lower acquisition cost.

B.5. References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Upadacitinib for treating active ankylosing spondylitis ID3848

Clarification questions

December 2021

File name	Version	Contains confidential information	Date
ID3848_Upadacitinib_AS_ERG CQ Response [ACIC]	1.0	Yes	24.01.22

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Questions on the systematic literature review and decision problem

A1. For the clinical searches, why did the company request that the LILACS database was limited to English language?

Based on the results of the systematic literature review (SLR), the company believe that all relevant studies were identified and included, and therefore, we do not believe that restricting the search of the Literatura Latino Americana em Ciências da Saúde (LILACS) database to English language would have an impact. The search of the LILACS bibliographic database was the only search in the portfolio of resources searched for the submission to be limited to English language and the evidence for limiting searches to English language is mixed, with a recent study (2021) finding that a limit to English language has little impact on the effect estimates and conclusions of systematic reviews.[1] To confirm that this restriction would not have impacted the results of the SLR, we have re-run our search of LILACS, removing the language limit. The search annex is provided below. We did not identify any new studies, or study data. We hope that this addresses your concerns.

Database: LILACS

Database host: https://lilacs.bvsalud.org/en/

- ◊ Clarification questions

Data parameters: 1982 to present

Date of search: Jan 17 2022

Search Strategy: Search undertaken on title, abstracts and in subject field:

(((axial spondyloarthritis) OR (axspa) OR (ankylosing spondylitis)) AND (upadacitinib* OR adalimumab* OR certolizumab* OR etanercept* OR davictrel* OR golimumab* OR infliximab*or inflix* OR ixekizumab* OR tofacitinib* OR secukinumab* OR filgotinib* OR hulio* OR imraldi* OR hefiya* OR amgevita* OR idacio* OR hyrimoz* OR halimatoz* OR amsparity* OR erelzi* OR benepali* OR zessly* OR flixab* OR bimekizumab*))

Thirty-four records were downloaded to EndNote for checking. See Appendix A for the reasons for exclusion for each record.

A2. Why are the update searches conducted on 28th October 2021 not documented? (mentioned in the main company submission [Document B], B.3.1, p.27)

The updated searches were conducted on October 28, 2021 in line with the methods used for the previous SLRs, outlined in Appendix C of the company submission. The full details of the methods and results are provided below.

Search strategy

Databases were searched from March 28, 2021 to October 28, 2021. The literature searches were conducted across the following electronic databases:

- MEDLINE®, 1946 to present (OVID)
- MEDLINE In-Process & Other Non-Indexed Citations (OVID)
- MEDLINE Epub Ahead of Print (OVID)
- Embase, 1980 to present (OVID)
- Latin American and Caribbean Health Sciences Literature (LILACS) database, 1982 to present (VHL)—English only publications
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
    - ◊ Clarification questions

- PubMed (NLM)—e-publications only[2]
- Database of Abstracts of Reviews of Effects (DARE) (CRD)
- Health Technology Assessment (HTA) database (INAHTA)
- International HTA (INAHTA) database
- Conference Proceedings Citation Index-Science (CPCI-S), 1990 to present (Web of Science, Clarivate Analytics)

In addition to bibliographic databases, several non-database sources were also searched:

- Trial registries:
    - ClinicalTrials.gov
    - EU Clinical Trials Register
    - World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)
- Websites:
    - The National Institute for Health and Care Excellence (NICE)
    - Scottish Medicine Consortium (SMC)
    - Pharmaceutical Benefits Advisory Committee (PBAC) Institute for Quality and Efficiency in Healthcare (IQWiG)
    - Canadian Agency for Drugs and Technologies in Health (CADTH)

Bibliographies of relevant systematic reviews or meta-analyses were hand-searched for applicable primary publications.

Embase and CPCI-S were searched to identify conference abstracts from proceedings indexed in these databases. The database search was conducted from March 2021 to October 2021, to align with the timeframe of the manual search. To supplement this search, hand-searching of conference abstracts from the past six months (March 2021–October 2021) from the following proceedings was conducted:

- European League Against Rheumatism (EULAR)
- American College of Rheumatology (ACR)
- British Society of Rheumatology (BSR)
    - ◊ Clarification questions

The complete original search strategy along with the number of search results are reported in Appendix B.

Inclusion and exclusion criteria

Eligibility criteria have been applied following the PICOS framework (participants, interventions, comparisons, outcomes, and study design), in line with PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidance.[3] The PICOS framework is used in selecting clinical trials for a literature review and was adapted to meet the study objectives. Table 1 and Table 2 of Appendix C from the Company Submission detail the eligibility criteria for the clinical and economic SLR updates, respectively.

Selection process

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded into Endnote version X9 and duplicated references were removed. Titles and abstracts identified by the search strategy were independently assessed for possible eligibility by two reviewers in line with the PICOS criteria. Studies that did not meet eligibility criteria were excluded. For citations that could potentially meet the eligibility criteria, full texts were retrieved, and the eligibility criteria applied. Any discrepancies between the two reviewers were resolved by mutual discussion. Reasons for exclusion were documented and the results of the literature search are presented in the form of a PRISMA flow diagram.

Results of search strategy for review of clinical and economic evidence

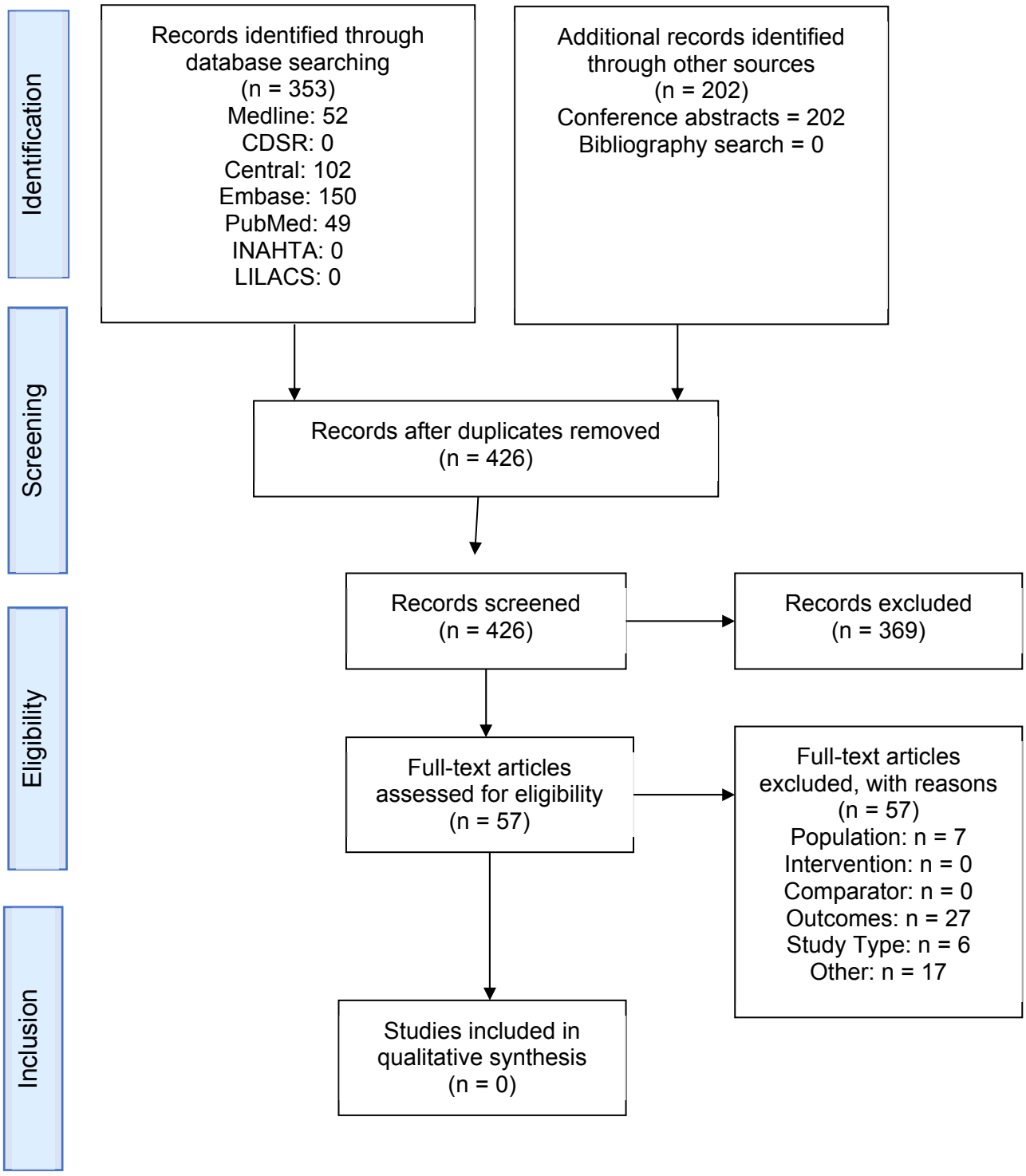
- ◊ Clarification questions

presents an overview of study flow for the updated clinical SLR search. A total of 353 studies were identified from database searches, together with 202 studies identified from additional sources. After removing duplicates, 426 studies were screened, of which 369 studies were excluded. Of the 57 studies remaining, full-text articles were retrieved, and 57 studies were excluded based on the eligibility criteria. There were no studies for data extraction.

Error! Reference source not found. presents an overview of study flow for the updated economic SLR. A total of 88 additional studies were identified from the database searches, no studies were identified from additional sources. After removal of duplicates, 76 studies were screened, of which 63 studies were excluded. Of the 13 studies remaining, full text articles were retrieved, and 13 studies excluded based on the eligibility criteria. There were no studies for data extraction.

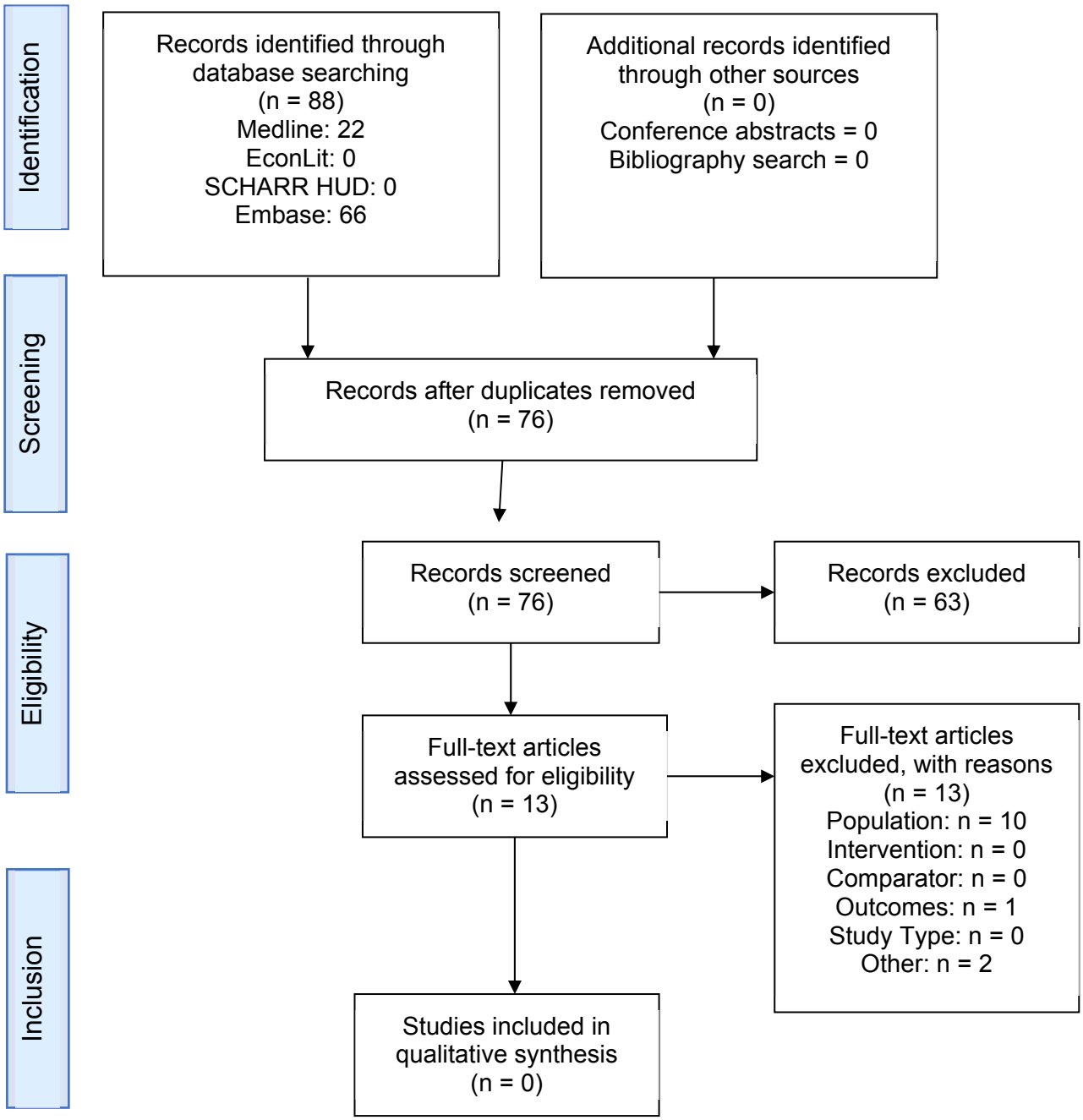
- Clarification questions

Figure 1. PRISMA diagram: systematic review of clinical studies from March 2021 to October 2021



◊ Clarification questions

Figure 2. PRISMA diagram: systematic review of economic studies from March 2021 to October 2021



◊ Clarification questions

A3. Why are terms for some of the biosimilars (below) not used in the clinical searches? Please provide assurance no relevant evidence has been missed.

- **Adalimumab: Kromeya, Solymbic, Yuflyma, PF-06410293**
- **Etanercept: Nepexto, BX2922, Etacept, Etanar, GP2013, PRX-106, Yisaipu, Eticovo, Lifmior**

In order to examine whether the omission of these biosimilars from the SLR search terms impacted the results, we re-ran searches in MEDLINE and Embase (Ovid interfaces). We have provided the search annexes for each database in Appendix C.

In short, we identified three study records that were not identified by our original and updated searches. None of these were eligible for inclusion in our review. Therefore, we do not believe that any relevant evidence was missed from the review.

Adalimumab: Kromeya, Solymbic, Yuflyma, PF-06410293

Please see line 7 of the MEDLINE search (n=0) and lines 11 and 12 of the Embase search (lines 11 and 12 both return n=3,594, meaning no unique records were identified between the searches). N=0 unique records. This demonstrates that no relevant evidence has been missed.

Etanercept: Nepexto, BX2922, Etacept, Etanar, GP2013, PRX-106, **Yis**aipu, Eticovo, Lifmior

Please see line 15 of the MEDLINE search and line 20 of the Embase search. The two items returned by MEDLINE, and the three by Embase, were de-duplicated (-2) leaving three records for screening. We screened these to the screening criteria of the review. No records were eligible for inclusion, for the reasons set out below (**Error! Reference source not found.**).

◊ Clarification questions

Table 1. Etanercept biosimilars screening outcome (n=3)

#	Citation	Reason for exclusion
1.	Huang, Z., et al. (2018). "Efficacy of Yisaipu tapering in the treatment of ankylosing spondylitis. [Chinese]." National Medical Journal of China **98(15)**: 1158-1161.	Ineligible study design (retrospective observational study)
2.	Zhao, M., et al. (2017). "The effect and safety of yisaipu (yisaipu) in the treatment of patients with nonradiographic axial spondyloarthritis in China." Annals of the Rheumatic Diseases **76(Supplement 2)**: 351-352.	Excluded based on population, studies patients with nr-axSpA
3.	Zhao, Z., et al. (2019). "Correlation between magnetic resonance imaging (MRI) findings and the new bone formation factor Dkk-1 in patients with spondyloarthritis." Clinical Rheumatology **38(2)**: 465-475.	Excluded based on population, studies patients with SpA, but does not specify AS

Questions on the decision problem

A4. Please clarify the proposed positioning of upadacitinib in the treatment pathway. Given the lack of comparisons with anti-TNFs, the ERG interprets the main company submission as proposing that upadacitinib be considered after an anti-TNF has already been tried (or it may be considered first-line if anti-TNFs are contraindicated). If this is incorrect, and upadacitinib is being proposed as an alternative to anti-TNFs (i.e. first-line), please provide cost-comparisons with anti-TNFs and make a case for positioning at this line of therapy. Please note that previous appraisals of biologic drugs in this disease area have explored the inclusion of class effects across anti-TNF treatments in the NMAs (see for example TA383).

Secukinumab is recommended by NICE, within its marketing authorization, as an option for treating active AS in adults whose disease has responded inadequately to conventional therapy (NSAIDs) or TNF-alpha inhibitors. Internal market research, included in our submission, indicates that secukinumab continues to hold a significant market share within the biologic naïve population, which would indicate use outside of just TNF contra-indicated patients. Clinician feedback has confirmed that the most relevant comparator for upadacitinib would be IL-17s (both secukinumab and ixekizumab) in either the biologic naïve or experienced populations. As such, this is the basis of our clinical and cost comparison in biologic naïve patients.

A5. PRIORITY QUESTION: Clinical trial evidence is available for two alternative JAK inhibitors, tofacitinib and filgotinib in this same indication. Please

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comment on the plausibility of a common effect or of a class effect on i) the effectiveness and ii) safety, across all these agents, which could make evidence on these alternative drugs relevant to the current appraisal. Note that, on safety, the FDA has issued a warning on all JAKs based solely on evidence on tofacitinib, explicitly considering the evidence exchangeable across treatments.[4] Please also consider the implications of this for the evidence and models used in the NMAs.

Filgotinib currently is not licensed in the UK for AS and is not scheduled for appraisal by NICE, so is not a relevant comparator in the UK. While tofacitinib is undergoing concurrent NICE appraisal, tofacitinib is not included in the scope of this appraisal, so discussion of the clinical evidence and a potential class effect is not appropriate.

With regards to safety profile, the FDA recognises that upadacitinib and baricitinib have not been studied in trials similar to the tofacitinib safety trial (ORAL SURVEILLANCE); however, as upadacitinib and baricitinib shares mechanisms of action with tofacitinib, the FDA believes they may have similar risks. Of note, the communication was not based on any safety data for upadacitinib which does not show increased risks of these events. ORAL SURVEILLANCE was conducted in a rheumatoid arthritis (RA) patient population enriched for patients over 50 years and with at least 1 cardiovascular risk factor; there has not been a similar study to ORAL SURVEILLANCE performed in AS or any other disease state beyond RA. Therefore, the risk for these events in another patient population such as AS or with other JAK inhibitors has not been evaluated in a similar fashion and it would not be appropriate to extrapolate to other indications where risk factors may differ depending on the patient population. In the absence of direct head-to-head JAK inhibitor studies, the benefit-risk (efficacy and safety) profile of one JAK inhibitor can also not be extrapolated to the entire JAK inhibitor class.

JAK inhibitors are a drug class of small molecules that target the same family of kinases, but each has distinct differences in its chemical structure and pharmacologic properties. Therefore they cannot be compared directly. The different chemical structure, pharmacokinetic/pharmacodynamic (half-lives), drug metabolism and elimination pathways may be associated with different clinical outcomes and

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each JAK inhibitor should be assessed individually based on its own clinical evidence and unique clinical profile.

Selective JAK inhibition implies that there is a greater inhibitory potency for one JAK isoform versus another at a given concentration.[5,6] Selective inhibition is dependent on relative potency, dose, and exposure; as exposure increases the inhibitory profile may become broader.[7,8] Upadacitinib, baricitinib, tofacitinib and filgotinib are all JAK inhibitors with differing selectivity profiles. Upadacitinib was engineered to have greater selectivity for JAK1 over other members of the JAK family, implying a greater inhibitory potency for JAK1 versus other isoforms at a given concentration.[5,6] 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.[9] Existing evidence does not allow for conclusions to be drawn regarding the impact of a certain JAK selectivity profile on a therapy's overall benefit-risk profile. Additionally different types of cellular and biochemical assays may be used to determine selectivity profiles for JAK inhibitors, making direct comparisons of relative selectivity difficult. As mentioned, no controlled, randomised, head-to-head clinical trials have been conducted to compare the efficacy and safety of upadacitinib to another JAK inhibitor. Therefore, no comparisons to the safety and efficacy of upadacitinib to the safety and efficacy of tofacitinib can be made.

Upadacitinib is currently approved in RA, Psoriatic arthritis (PsA), AS (15mg) and atopic dermatitis (AD) (15mg and 30mg) in major markets worldwide, including the EU and Japan. Regulatory authorities in over 60 countries, including the EMA and Japan have reviewed the totality of available data with upadacitinib 15 mg, which supported approval in RA in those countries and regulatory authorities in over 40 countries, including the EMA and Japan have reviewed the totality of available data with upadacitinib 15 mg, which supported approval in PsA. Similarly, the EMA and other regulatory agencies also approved upadacitinib 15 mg for AS and most recently, upadacitinib 15 mg and 30 mg for AD. We continue to assess the safety profile of upadacitinib across approved indications, remain committed to constant and transparent communication of these data and continue to work closely with health authorities across the world.

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Questions on the clinical trial evidence

A6. PRIORITY QUESTION: The MHRA and FDA have both recently concluded that there is an increased risk of serious adverse events such as heart attack, stroke, cancer, blood clots, death and other SAEs with tofacitinib.[10-12] The FDA considers that since upadacitinib shares the mechanism of action with tofacitinib, it may have similar risks as seen in the tofacitinib safety trial.[4] In light of this, please:

a) ***Comment on these important safety issues and their likely implications on ankylosing spondylitis JAK inhibitor treatment decisions in the NHS.***

As mentioned above, the ORAL SURVEILLANCE study was conducted in an RA patient population using tofacitinib and therefore, this data cannot be extrapolated to an AS patient population or a different JAK inhibitor. Therefore, it is difficult to make direct efficacy or safety comparisons in this patient population.

There are currently several challenges in the treatment of AS due to the limited number of treatment options available, especially regarding the limited mechanisms of action and mode of administration. Therefore, clinicians welcome a new mode of action as well as an oral therapy oppose to a subcutaneous injection. Clinicians comment that in terms of rheumatology, on average, AS patients are younger and tend to have fewer comorbidities and risk factors compared to RA patients. As standard clinical practice, all health care professionals would follow local guidelines and recommendations on the SmPC of JAKi, including upadacitinib, to ensure they take a history and assess all risk factors before initiating treatment. It is important to bear in mind the EULAR guidelines (EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders:2015/16 update) state that a rheumatologist is responsible for monitoring all AS patients for signs of cardiovascular involvement to ensure the appropriate disease management strategies are implemented.

The safety profile of upadacitinib with up to 4.5 years of exposure in patients (RA, PsA and AS) remained unchanged over long-term treatment compared with previous analyses.[13] The safety profile of upadacitinib 15 mg in patients with PsA and AS was consistent with that observed in RA, with no new safety signals observed.[14,15] After

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up to 2 years of follow-up, there were no serious infections, non-melanoma skin cancer (NMSC), MACEs or VTEs reported in the SELECT-AXIS 1 trial.[16] In SELECT-AXIS 1, the proportion of patients with AEs was generally similar in the upadacitinib and placebo groups. No serious infections, malignancies, anaemia, lymphopenia, herpes zoster, renal dysfunction, adjudicated major adverse cardiovascular events, venous thromboembolic events, or deaths were reported, and haemoglobin levels remained consistent throughout the first 14 weeks of the study. No new safety findings, serious infections, active tuberculosis, adjudicated MACE, lymphoma, non-melanoma skin cancer, renal dysfunction, or gastrointestinal perforations were observed over 2 years.

The same safety profile was also observed during SELECT-AXIS2, where the rate of overall AEs was similar between the upadacitinib and placebo arms. For AEs leading to discontinuation, none were reported in the upadacitinib arm compared to [redacted] ([redacted] %) in the placebo arm. No deaths were reported. Serious infections and herpes zoster were reported in the upadacitinib arm ([redacted] % and [redacted] %, respectively compared to 0 in the placebo arm). Four of the five serious infections were COVID-19 or COVID-19 pneumonia. Neither herpes zoster events were serious, did not lead to treatment discontinuation, and involved a single dermatome. There were no events of opportunistic infection, non-melanoma skin cancer, lymphoma, adjudicated GI perforation, renal dysfunction, active tuberculosis, adjudicated MACE or VTE reported.

The safety profile of upadacitinib aligns with the safety profiles previously observed with IL-17A inhibitors. The rates of adverse events reported in the SELECT-AXIS1 and 2, MEASURE1-5 and COAST-V and COAST-W trials for upadacitinib, secukinumab and ixekizumab at the short-term timepoint (weeks 14-16) and long-term timepoint (weeks 52-104) are presented in **Error! Reference source not found.** and Table 4, respectively. The rates of adverse events, serious adverse events and discontinuation due to adverse events were similar between upadacitinib, secukinumab and ixekizumab at both the short and longer term timepoints. Similarly, the types and rates of these adverse events were similar, with no patients reporting cases of VTE and MACE and only 1 (0.8%) patient reporting malignancy.

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During an advisory board meeting held by AbbVie, the safety profile of upadacitinib for the treatment of AS using the safety results from the SELECT-AXIS1 trial was discussed. The clinicians consulted, who were all experts in the treatment of AS in the UK, agreed that the safety profile of upadacitinib was considered to be good with no major safety concerns.[17]

b) Provide details of any published, or ongoing, upadacitinib safety studies which cover populations with diseases other than ankylosing spondylitis.

We currently have safety data for upadacitinib across the following Immune-Mediated Inflammatory Diseases: Atopic Dermatitis (AD), Ulcerative Colitis (UC) AS, Rheumatoid arthritis (RA), Ankylosing Spondylitis (AS) and Psoriatic Arthritis (PsA); please see publication list below. With regards to rheumatology, we have conducted an integrated safety analysis which covers distinct analyses across three separate clinical trial programs in RA, PsA, and AS; please see attached Burmester G et al. Arthritis Rheumatol 2021; 73 (suppl10), Abstract 1691. In total, 5620 patients were included in this analysis, with 4298 of the patients receiving ≥1 dose of upadacitinib 15 mg (RA, N=3209; PsA, N=907; AS, N=182). In this integrated long-term safety analysis (up to 4.5 years of study drug exposure), the rate of malignancies (excluding NMSC) was similar across all treatment groups (upadacitinib 15 mg and adalimumab 40 mg eow) and patient populations. The number of malignancies excluding NMSC in patients exposed to upadacitinib 15 mg was not higher than would be expected for the general population based on the US National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database (standardized incidence ratio: 1:1). Similar rates of adjudicated MACE and adjudicated VTE were observed across all treatments in RA and PsA, with no events reported in AS.

Please see summary table of the safety risks that were highlighted as of interest (**Error! Reference source not found.**).

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Table 2. Summary table of selected safety risks

Event Rate/100PY (95%CI)	Upadacitinib 15mg (N=3209, 7023.8 PY)	Adalimumab 40mg (N=579, 1051.8 PY)	MTX Monotherapy (N=314, 637.4 PY)
MACE	0.4 (0.3-0.6)	0.3 (0.1-0.8)	0.3 (0.0-1.1)
Malignancies (excluding NMSC)	0.8 (0.6-1.1)	0.8 (0.3-1.5)	0.9 (0.3-2.0)
VTE	0.5 (0.3-0.6)	0.5 (0.2-1.1)	0.3 (0.0-1.1)
Deaths	0.4 (0.3-0.6)	0.4 (0.1-1.0)	0.2 (0.0-0.9)

We continue to assess the ongoing safety profile of upadacitinib across indications and remain committed to working closely with health authorities across the world. The benefit-risk profile of upadacitinib remains favourable for the approved indications under investigation. Both clinical trials and post-marketing safety data of upadacitinib have been continuously monitored and assessed through vigorous approaches, including regular periodic safety update reports in which malignancies (excluding NMSC), MACE and VTE are assessed, in addition to standardised surveillance activities. These important potential risks are also being further evaluated in post authorisation long term safety studies for upadacitinib across all indications.

Specifically, AbbVie is conducting post-approval safety studies through registries in the EU and the US as part of the agreed upon Risk Management Plan with the EMA. In addition to the long-term extension of our clinical trials, we are also conducting PMOS (Post-Marketing observational studies) and routine safety monitoring (e.g., MHRA Yellow card safety reporting). The list below are the post-authorisation safety studies/activities and European registries which will and are continually collecting safety data.

With regards to the long-term extension of our clinical trials, we would like to highlight that the ongoing upadacitinib clinical development program has a 10-year long-term TNFi active comparator (adalimumab) study in RA and a 5-year long-term TNFi active comparator (adalimumab) study in PsA. This allows the presentation of safety data for upadacitinib in context with adalimumab (SELECT-COMPARE in RA and SELECT-PsA 1 in PsA). Safety data from the adalimumab arm allow us to present long-term safety data for upadacitinib in the context of a standard of care therapy. In terms of other activities, a rigorous approach is being taken to evaluate the safety of upadacitinib in the treatment of moderately to severely active RA in the

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post-marketing setting. This is composed of two prospective observational cohort studies to compare the incidence of malignancies, VTEs, MACE, and serious infection events (SIEs) in patients treated with upadacitinib relative to patients treated with biologic medications. This approach includes leveraging existing registries both in the US (CorEvitas) and in the EU (collaboration with 5 European based registries) and will include up to 8 years of patient follow up. These studies are designed to identify an increased risk for certain safety events including MACE and malignancies as well as VTEs.

List of published safety data for Upadacitinib

1) Cohen, SB, van Vollenhoven R, Curtis JR, et al. June 2-5, 2021; Virtual Congress. Poster POS0220.
2) Deodhar A, van der Heijde D, Siper J, et al. Arthritis Rheumatol 2021
3) Fleischmann R, Pangan AL, Song I, et al. Arthritis Rheumatol. 2019;71 (11):1788-1800.
4) Rubbert-Roth A, Enejosa J, Pangan AL, et al. N Engl J Med. 2020;383:1511-1521.
5) Smolen JS, Pangan AL, Emery P, et al. Lancet. 2019;393(10188):2303-2311.
6) Burmester G et al. Arthritis Rheumatol 2021; 73 (suppl10);
7) Van Vollenhoven R et al. Arthritis Rheumatol 2020; 72:1607–1620;
8) Burmester GR et al. Lancet 2018;391:2503–2512;
9) Fleischman RM et al. Ann Rheum Dis 2019;78:1454–1462;
10) Genovese M et al. Lancet 2018;391:2513–2524;
11) Mease PJ et al. Ann Rheum Dis 2020;80:312–320;
12) McInnes IB et al. N Engl J Med 2021;384:1227–1239.
13) Panaccione R et al. Oral presentation at United European Gastroenterology Week, 3–5 October 2021 [LB11];
14) Burmester GR et al. Abstract presented at: EULAR 2021, 2–5 June 2021 [Abstract 395];
15) Simpson EL et al. Poster presented at: DERM 2021, 5–8 August 2021;

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16) Silverberg JI et al. J Allergy Clin Immunol 2021. [Epub ahead of print]. DOI: 10.1016/j.jaci.2021.07.036.

List of ongoing safety activities

1) Long-term comparative safety cohort study of upadacitinib use for the treatment of RA in the US (CorEvitas)
2) Long-term comparative safety cohort study of upadacitinib use for the treatment of RA in the US – Biosample Sub-study (CorEvitas)
3) Drug utilisation study of upadacitinib in Europe to evaluate the effectiveness of additional risk minimisation measures
4) Sweden (ARTIS) - Swedish Rheumatology Quality Register (SRQ) and its linkage to other national Swedish registers (the Anti Rheumatic Treatment in Sweden safety monitoring programme)
5) Denmark (DANBIO) - Danish Registry of Biological Therapy linked to other national Danish registers
6) United Kingdom (BSRBR-RA) - British Society for Rheumatology Biologics Register for Rheumatoid Arthritis
7) Spain (BIOBADASER) - Spanish Registry for Adverse Events of Biological Therapy and Targeted Synthetic DMARD in Rheumatic Diseases
8) Germany (RABBIT) - RA Biologics Register
9) AD-VISE (global AD study)

c) Provide any FDA documentation relating to the approval of upadacitinib for psoriatic arthritis including information relating to the drug's safety profile.[18]

Documentation related to the FDA's approval of upadacitinib for psoriatic arthritis has been provided separately.

A7. Table 30 in the main company submission reports treatment-emergent adverse events at the end of study period (104 weeks) for SELECT-AXIS1. For SELECT-AXIS2 these data are only reported at 14 weeks in the main company

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submission and CSR. Please present these longer-term safety data for SELECT-AXIS2, if available.

The SELECT-AXIS2 clinical trial is currently ongoing and so longer-term safety data beyond 14 weeks is not currently available.

The company believes that the long-term safety data from SELECT-AXIS1 from the 104 week timepoint is representative of the safety profile for upadacitinib in patients with AS, regardless of their previous bDMARD experience. This was confirmed by UK clinicians at an advisory board held by AbbVie.[17] The safety profile of upadacitinib was similar in the SELECT-AXIS1 trial at both the week 14 and week 104 timepoints, with no new safety concerns raised at this later timepoint, and no serious infections, renal dysfunction, adjudicated major adverse cardiovascular events, venous thromboembolic events or death reports during either time period. The safety profile of upadacitinib is also similar to that observed with TNFi and IL-17A inhibitors for the treatment of AS (Table 3 and Table 4).[19-22]

A8. PRIORITY QUESTION: Please present a formal synthesis (e.g. an NMA) of discontinuation rates due to adverse events, adverse events and serious adverse events – see e.g. the meta-analysis in Yin et al (2020).[23] Please consider a class effect for IL-17s if appropriate (see also question A5). If this is not possible, please present tables comparing the AE rates for upadacitinib, secukinumab, and ixekizumab.

Clinical expert opinion was sought on the comparative safety profiles of upadacitinib and IL-17 therapies (secukinumab and ixekizumab). Based on a review of the adverse event data from the respective clinical trials, clinician feedback indicated that a safety NMA was not necessary. Moreover, there are technical considerations with the development of a safety NMA in this instance. For example, there are differences in the reporting of adverse events with some studies reporting as number of cases per 100 patient-years and others reporting percentage of events. As such, a naïve comparison of AE rates is presented.

Comparison of adverse event rates

The rates of adverse events reported in the SELECT-AXIS1-2, MEASURE1-5 and COAST-V and COAST-W trials for upadacitinib, secukinumab and ixekizumab at the

short-term timepoint (weeks 14-16) and long-term timepoint (weeks 52-104) are presented in Table 3 and Table 4, respectively. The rates of adverse events, serious adverse events and discontinuation due to adverse events were similar between upadacitinib, secukinumab and ixekizumab at both the short and longer term timepoints.

The rate of adverse events reported was [redacted] % for upadacitinib at week 14 and 45-68% for secukinumab at week 16. It was not reported for ixekizumab. Similarly the rate of serious adverse events ([redacted] % for upadacitinib, 1-6% for secukinumab and 1-4% for ixekizumab) and the rate of discontinuation due to adverse events ([redacted] % for upadacitinib, 0-5% for secukinumab and 0-9% for ixekizumab) was also similar for each of the treatments at weeks 14-16.

At the longer term timepoint, the rate of serious adverse events were also similar between the treatments ([redacted] % for upadacitinib, 5-9% for secukinumab and 1-5% for ixekizumab), despite the variation in timepoint from week 52 to 104. The rate of discontinuation due to adverse events was also similar between treatments over the same time periods ([redacted]% for upadacitinib, 2-4% for secukinumab and 1-6% for ixekizumab).

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Table 3. Adverse event rates at weeks 14-16 for upadacitinib, secukinumab and ixekizumab

	SELECT-AXIS1 (Week 14) UPA n (%)	SELECT-AXIS2 (Week 14) UPA n (%)	MEASURE1 (Week 16) SEC n (%)	MEASURE2 (Week 16) SEC n (%)	MEASURE3 (Week 16) SEC n (%)	MEASURE3 (Week 16) SEC n (%)	MEASURE4 (Week 16) SEC n (%)	MEASURE5 (Week 16) SEC n (%)	COAST-V (Week 16) IXE n (%)	COAST-V (Week 16) IXE n (%)	COAST-W (Week 16) IXE n (%)	COAST-W (Week 16) IXE n (%)
Reference	**Van der Heijde 2019[16]**	**CSR[25]**	**Beaten 2015[24]**	**Beaten 2015[24]**	**Pavelka 2017[20]**	**Pavelka 2017[20]**	**Kivitz 2018[26]**	**Huang 2020[27]**	**Van der Heijde 2018[28]**	**Van der Heijde 2018[28]**	**Deodhar 2019[29]**	**Deodhar 2019[29]**
Dose	**15 mg QD**	**15 mg QD**	**Pooled**	**Pooled**	**300 mg**	**150 mg**	**150 mg no LD**	**150 mg**	**80 mg Q2W**	**80 mg Q4W**	**80 mg Q2W**	**80 mg Q4W**
n	**93**	**211**	**249**	**145**	**76**	**74**	**116**	**304**	**83**	**81**	**98**	**114**
Any adverse event	58 (62)	[redacted]	170 (68)	89 (61)	34 (44.7)	34 (45.9)	72 (62.1)	206 (67.8)	-	-	-	-
Serious adverse event	1 (1)	[redacted]	5 (2)	8 (6)	1 (1.3)	0	2 (1.7)	10 (3.3)	1 (1)	1 (1)	3 (3.1)	4 (3.5)
Adverse event leading to discontinuation	2 (2)	[redacted]	3 (1)	7 (5)	0	0	1 (0.9)	2 (0.7)	3 (4)	0	3 (3.1)	10 (8.8)
Any infection	19 (20)	[redacted]	75 (30)	46 (32)	-	-	-	-	17 (20)	16 (20)	23 (23.5)	34 (29.8)
Serious infection	0	[redacted]	-	-	-	-	0 (0.9)	4 (1.3)	1 (1)	1 (1)	0	2 (1.8)
Malignancy	0	[redacted]	-	-	0	0	-	-	0	0	0	1 (0.9)
Neutropenia	1 (1)	[redacted]	0	0	0	3 (4.1)	0	0	11 (14)	8 (11)	-	-
Cardiovascular events (adjudicated)	0	[redacted]	0	1 (<1)	-	-	0	0	-	-	1 (1.0)	0
Death	0	[redacted]	0	1 (<1)	0	0	0	0	0	0	1 (1.0)	0
IXE: ixekizumab; SEC: secukinumab; UPA: upadacitinib												

Table 4. Adverse event rates at weeks 52-104 for upadacitinib, secukinumab and ixekizumab

	SELECT-AXIS1 (Week 104) UPA Rate per 100 patient-years	MEASURE1 (Week 52) SEC Rate per 100 patient-years	MEASURE2 (Week 52) SEC Rate per 100 patient-years	MEASURE3 (Week 52) SEC Rate per 100 patient-years	MEASURE3 (Week 52) SEC Rate per 100 patient-years	MEASURE4 (Week 104) SEC n (%)	MEASURE5 (Week 52) SEC n (%)	COAST-V (Week 52) IXE n (%)	COAST-V (Week 52) IXE n (%)	COAST-W (Week 52) IXE n (%)	COAST-W (Week 52) IXE n (%)
Reference	**CSR[25]**	**Beaten 2015[24]**	**Beaten 2015[24]**	**Pavelka 2017[20]**	**Pavelka 2017[20]**	**Kivitz 2018[26]**	**Huang 2020[27]**	**Dougados 2020[21]**	**Dougados 2020[21]**	**Dougados 2020[21]**	**Dougados 2020[21]**
Dose	**15 mg QD**	**Pooled**	**Pooled**	**300 mg**	**150 mg**	**150 mg no LD**	**150 mg**	**80 mg Q2W**	**80 mg Q4W**	**80 mg Q2W**	**80 mg Q4W**
n	**182**	**360**	**211**	**113**	**110**	**116**	**453**	**78**	**79**	**98**	**90**
Any adverse event	[redacted]	291 (203.2)	175 (212.9)	83 (152.7)	90 (179.2)	98 (83.8)	364 (80.4)	-	-	-	-
Serious adverse event	[redacted]	35 (8.3)	17 (7.1)	6 (4.8)	6 (4.8)	11 (9.4)	33 (7.3)	4 (5.1)	3 (3.8)	2 (2.0)	1 (1.1)
Adverse event leading to discontinuation	[redacted]	15	9	4 (3.5)	4 (3.6)	5 (4.3)	10 (2.2)	1 (1.3)	2 (2.5)	4 (4.1)	5 (5.6)
Any infection	[redacted]	187 (66.1)	111 (73.7)	-	-	-	-	25 (32.1)	25 (31.6)	29 (29.6)	33 (36.7)
Serious infection	[redacted]	-	-	-	-	1 (0.9)	9 (2.0)	0	1 (1.3)	0	1 (1.1)
Malignancy	[redacted]	-	-	1 (0.9)	1 (0.9)	-	-	0	0	0	0
Neutropenia	[redacted]	4 (0.9)	1 (0.4)	1 (0.9)	3 (2.7)	0	2 (0.4)	-	-	-	-
Cardiovascular events (adjudicated)	[redacted]	2 (0.5)	1 (0.4)	-	-	-	1 (0.2)	0	0	0	0
Death	[redacted]	0	1	0	0	0	0	0	0	3 (3.1)	1 (1.1)

IXE: ixekizumab; SEC: secukinumab; UPA: upadacitinib

A9. Please present Tables 15 and 21 of the main company submission with results added for BASDAI change from baseline.

During SELECT-AXIS1 and SELECT-AXIS2, BASDAI change form baseline (CFB) was not a ranked endpoint, and therefore, was not included in the multiplicity adjusted analysis. The results for BASDAI CFB from SELECT-AXIS1 and SELECT-AXIS2 at week 14 have been included in Table 5 and Table 6, respectively.

Table 5. Summary of secondary endpoints from SELECT-AXIS1 at week 14, including BASDAI CFB and ranked secondary endpoints

Endpoint	N	Within group point estimate (95% CI)	Between group difference (Upadacitinib – placebo)		
			Point estimate (95% CI)	Nominal P-Value	Multiplicity adjusted results
BASDAI change from baseline					
Placebo	84	[redacted]	-	<0.001	Not applicable
Upadacitinib	84	[redacted]			
ASDAS (CRP) change from baseline					
Placebo	84	[redacted]	[redacted]	<0.001	Significant
Upadacitinib	84	[redacted]			
SPARCC Score – Spine, change from baseline					
Placebo	60	[redacted]	[redacted]	<0.001	Significant
Upadacitinib	68	[redacted]			
BASDAI50 response rate					
Placebo	94	[redacted]	[redacted]	0.002	Significant
Upadacitinib	93	[redacted]			
ASQoL change from baseline					
Placebo	88	[redacted]	[redacted]	0.016	Non-significant
Upadacitinib	88	[redacted]			
ASAS partial remission response rate					
Placebo	94	[redacted]	[redacted]	< 0.001	Significant
Upadacitinib	93	[redacted]			
BASFI change from baseline					
Placebo	86	[redacted]	[redacted]	0.001	Significant
Upadacitinib	86	[redacted]			
BASMI change from baseline					
Placebo	89	[redacted]	[redacted]	0.030	Non-significant
Upadacitinib	89	[redacted]			
MASES (for subjects with baseline enthesitis) change from baseline					
Placebo	51	[redacted]	[redacted]	0.049	Non-significant
Upadacitinib	50	[redacted]			
WPAI overall work impairment change from baseline					
Placebo	53	[redacted]	[redacted]	0.190	Non-significant
Upadacitinib	55	[redacted]			
ASAS health index change from baseline					
Placebo	88	[redacted]	[redacted]	0.007	Non-significant
Upadacitinib	88	[redacted]			

ASAS: assessment of ankylosing spondylitis; ASDAS: ankylosing spondylitis disease activity score; ASQoL: ankylosing spondylitis quality of life; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis mobility index; CI: confidence

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interval; CRP: c-reactive protein; MASES: Maastricht ankylosing spondylitis enthesitis score; SPARCC: Spondyloarthritis Research Consortium of Canada; WPAI: work productivity and activity impairment questionnaire.

Source: SELECT-AXIS1 CSR[25]

Table 6. Summary of secondary endpoints from SELECT-AXIS2 at week 14, including BASDAI CFB and ranked secondary endpoints

		Endpoint	Placebo n=209	Upadacitinib 15mg QD n-211	Upadacitinib – Placebo (95% CI)	P-Value[a]
Primary		ASAS40	18.2%	44.5%	[redacted]	<0.0001*
Non-ranked secondary endpoints		BASDAI CFB	[redacted]	[redacted]	[redacted]	<0.0001
Ranked key secondary endpoints	1	ASDAS (CRP)	[redacted]	[redacted]	[redacted]	<0.0001*
	2	MRI Spine SPARCC[b]	[redacted]	[redacted]	[redacted]	<0.0001*
	3	BASDAI50	[redacted]	[redacted]	[redacted]	<0.0001*
	4	ASAS20	[redacted]	[redacted]	[redacted]	<0.0001*
	5	ASDAS (CRP) inactive disease	[redacted]	[redacted]	[redacted]	<0.0001*
	6	Total back pain	-1.47	-3.00	[redacted]	<0.0001*
	7	Nocturnal back pain	[redacted]	[redacted]	[redacted]	<0.0001*
	8	ASDAS (CRP) low disease activity	[redacted]	[redacted]	[redacted]	<0.0001*
	9	BASFI (Function)	-1.09	-2.26	[redacted]	<0.0001*
	10	ASAS partial remission	[redacted]	[redacted]	[redacted]	<0.0001*
	11	ASQoL	[redacted]	[redacted]	[redacted]	<0.0001*
	12	ASAS Health Index	[redacted]	[redacted]	[redacted]	<0.0001*
	13	BASMI (Mobility)	[redacted]	[redacted]	[redacted]	<0.0001*
	14	MASES (enthesitis)[c]	[redacted]	[redacted]	[redacted]	<0.0001*

Results for binary endpoints are based on NRI-MI analysis. Analyses for all continuous endpoints are for the change from baseline value. Results for continuous endpoints are based on MRMM, except for MRI and BASMI which use ANCOVA analysis.
a Unadjusted p-values are presented. * denotes multiplicity-controlled statistical significance at the pre-specified two sided 0.05 level.
b Summarised for patients with available baseline MRI data up to 3 days post first dose of study drug and available wee 14 MRI data up to the first dose of open-label period study drug
c Summarised for patients with presence of enthesitis at baseline (n=162 in placebo arm; n=148 in upadacitinib arm).
ASAS: assessment of ankylosing spondylitis; ASDAS: ankylosing spondylitis disease activity score; ASQoL: ankylosing spondylitis quality of life; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis metrology index; CI: confidence interval; CRP: C-reactive protein; MASES: Maastricht ankylosing spondylitis enthesitis score; MRI: magnetic resonance imaging; SPARCC: Spondyloarthritis Research Consortium of Canada;
Source: SELECT-AXIS2 CSR,[30] AbbVie press release 2021[31]

A10. Table 13 of the main company submission reports concomitant NSAID and csDMARDs use in SELECT-AXIS1 trial, whilst Table 20, page 54 report NSAID, csDMARDs and corticosteroid use at baseline. Please could you clarify for each trial the number and proportion of patients taking NSAIDs,

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corticosteroids and csDMARDs at (1) randomisation and (2) at weeks 0, 4, 8 & 14.

The number and proportion of patients taking NSAIDs, corticosteroids and csDMARDs at randomisation in the SELECT-AXIS1 and SELECT-AXIS2 trials is presented in Table 7.

As per the study protocols, concomitant medication use was only captured at baseline, and so this data is not available for the later timepoints. This is considered a standard approach for trials in AS. Further, the eligibility criteria for the trials stated that if patients were receiving concomitant csDMARDs, corticosteroids or NSAIDs, the patient must be on a stable dose for at least 28 days prior to the baseline visit, indicating that change in medications was not frequent.

Table 7. The proportion of patients taking concomitant medications during the SELECT-AXIS1 and SELECT-AXIS2 trials

		NSAIDs n (%)	Corticosteroids n (%)	csDMARDs n (%)
SELECT-AXIS1				
Randomisation	Upadacitinib	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
SELECT-AXIS2				
Randomisation	Upadacitinib	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]

A11. Please provide details on the type of NSAIDs, corticosteroids and csDMARDs taken by patients at (1) randomisation and (2) at weeks 0, 4, 8 & 14.

Details on the types of NSAIDs, corticosteroids and csDMARDs were only collected at randomisation and are presented in Table 8 and Table 9. As per the study protocols, concomitant medication use was only captured at baseline, and so this data is not available for the later timepoints. This is considered a standard approach for trials in AS. The eligibility criteria for the trials stated that if patients were receiving concomitant csDMARDs, corticosteroids or NSAIDs, the patient must be on a stable dose for at least 28 days prior to the baseline visit.

Table 8 Types of NSAIDs, corticosteroids and csDMARDs taken at baseline in SELECT-AXIS1

	Placebo n (%)	Upadacitinib n (%)	Total n (%)

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SELECT-AXIS1									
NSAIDs									
Any prior NSAID		[redacted]			[redacted]			[redacted]	
Aceclofenac		[redacted]			[redacted]			[redacted]	
Acemetacin		[redacted]			[redacted]			[redacted]	
Acetylsalicylic acid		[redacted]			[redacted]			[redacted]	
Arthrotec		[redacted]			[redacted]			[redacted]	
Celecoxib		[redacted]			[redacted]			[redacted]	
Delta-oxybuton		[redacted]			[redacted]			[redacted]	
Dexibuprofen		[redacted]			[redacted]			[redacted]	
Dexketoprofen trometamol		[redacted]			[redacted]			[redacted]	
Diclofenac		[redacted]			[redacted]			[redacted]	
Dioxaflex protec		[redacted]			[redacted]			[redacted]	
Etodolac		[redacted]			[redacted]			[redacted]	
Etoricoxib		[redacted]			[redacted]			[redacted]	
Flurbiprofen		[redacted]			[redacted]			[redacted]	
Ibuprofen		[redacted]			[redacted]			[redacted]	
Indomethacin		[redacted]			[redacted]			[redacted]	
Ketoprofen		[redacted]			[redacted]			[redacted]	
Lornoxicam		[redacted]			[redacted]			[redacted]	
Loxoprofen		[redacted]			[redacted]			[redacted]	
Meloxicam		[redacted]			[redacted]			[redacted]	
Metamizole		[redacted]			[redacted]			[redacted]	
Nabumetone		[redacted]			[redacted]			[redacted]	
Naproxen		[redacted]			[redacted]			[redacted]	
Nimesulide		[redacted]			[redacted]			[redacted]	
Olfen		[redacted]			[redacted]			[redacted]	
Pelubiprofen		[redacted]			[redacted]			[redacted]	
Phenylbutazone		[redacted]			[redacted]			[redacted]	
Piroxicam		[redacted]			[redacted]			[redacted]	
Proglumetacin		[redacted]			[redacted]			[redacted]	
Sulindac		[redacted]			[redacted]			[redacted]	
Tapentadol		[redacted]			[redacted]			[redacted]	
Tenoxicam		[redacted]			[redacted]			[redacted]	
Tiaprofenic acid		[redacted]			[redacted]			[redacted]	
Vimovo		[redacted]			[redacted]			[redacted]	
[redacted]									
Any prior csDMARD		[redacted]			[redacted]			[redacted]	
Apremalist		[redacted]			[redacted]			[redacted]	
Azathioprine		[redacted]			[redacted]			[redacted]	
Hydroxychloroquine		[redacted]			[redacted]			[redacted]	
Leflunomide		[redacted]			[redacted]			[redacted]	
Mesalazine		[redacted]			[redacted]			[redacted]	
Methotrexate		[redacted]			[redacted]			[redacted]	
Sulfasalazine		[redacted]			[redacted]			[redacted]	
[redacted]									
Any prior corticosteroids		[redacted]			[redacted]			[redacted]	
Betamethasone		[redacted]			[redacted]			[redacted]	
Deflazacort		[redacted]			[redacted]			[redacted]	
Delta-oxybuton		[redacted]			[redacted]			[redacted]	
Dexamethasone		[redacted]			[redacted]			[redacted]	
Methylprednisolone		[redacted]			[redacted]			[redacted]	
Prednisolone		[redacted]			[redacted]			[redacted]	
Prednisone		[redacted]			[redacted]			[redacted]	
Triamcinolone		[redacted]			[redacted]			[redacted]	

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Table 9. Types of NSAIDs, corticosteroids and csDMARDs taken at baseline in SELECT-AXIS2

	Placebo n (%)	Upadacitinib n (%)	Total n (%)
SELECT-AXIS2			
NSAIDs			
Any prior NSAID	[redacted]	[redacted]	[redacted]
Aceclofenac	[redacted]	[redacted]	[redacted]
Acemetacin	[redacted]	[redacted]	[redacted]
Acetylsalicylic acid	[redacted]	[redacted]	[redacted]
Acetylsalicylic acid; aluminium glycinate; magnesium carbonate	[redacted]	[redacted]	[redacted]
Acetylsalicylic acid; caffeine; paracetamol	[redacted]	[redacted]	[redacted]
Acetylsalicylic acid; magnesium hydroxide	[redacted]	[redacted]	[redacted]
Amtolmetin	[redacted]	[redacted]	[redacted]
Caffeine; carisoprodol; diclofenac sodium; paracetamol	[redacted]	[redacted]	[redacted]
Celecoxib	[redacted]	[redacted]	[redacted]
Chondroitin sulfate; glucosamine sulfate; ibuprofen	[redacted]	[redacted]	[redacted]
Dexketoprofen	[redacted]	[redacted]	[redacted]
Dexketoprofen trometamol	[redacted]	[redacted]	[redacted]
Diclofenac	[redacted]	[redacted]	[redacted]
Diclofenac epolamine	[redacted]	[redacted]	[redacted]
Diclofenac potassium	[redacted]	[redacted]	[redacted]
Diclofenac potassium; paracetamol' serrapeptase	[redacted]	[redacted]	[redacted]
Diclofenac sodium	[redacted]	[redacted]	[redacted]
Diclofenac sodium; lidocaine hydrochloride	[redacted]	[redacted]	[redacted]
Diclofenac sodium; misoprostol	[redacted]	[redacted]	[redacted]
Diclofenac sodium; omeprazole	[redacted]	[redacted]	[redacted]
Diclofenac sodium; paracetamol	[redacted]	[redacted]	[redacted]
Esomeprazole magnesium; naproxen	[redacted]	[redacted]	[redacted]
Etodolac	[redacted]	[redacted]	[redacted]
Etoricoxib	[redacted]	[redacted]	[redacted]
Flurbiprofen	[redacted]	[redacted]	[redacted]
Glucosamine; indomethacin	[redacted]	[redacted]	[redacted]
Ibuprofen	[redacted]	[redacted]	[redacted]
Imrecoxib	[redacted]	[redacted]	[redacted]
Indomethacin	[redacted]	[redacted]	[redacted]
Ketoprofen	[redacted]	[redacted]	[redacted]
Ketorolac	[redacted]	[redacted]	[redacted]
Ketorolac tromethamine	[redacted]	[redacted]	[redacted]
Lornoxicam	[redacted]	[redacted]	[redacted]
Loxoprofen	[redacted]	[redacted]	[redacted]
Loxoprofen sodium	[redacted]	[redacted]	[redacted]
Loxoprofen sodium dihydrate	[redacted]	[redacted]	[redacted]
Meloxicam	[redacted]	[redacted]	[redacted]
Metamizole	[redacted]	[redacted]	[redacted]
Metamizole sodium	[redacted]	[redacted]	[redacted]
Nabumetone	[redacted]	[redacted]	[redacted]
Naproxen	[redacted]	[redacted]	[redacted]
Naproxen sodium	[redacted]	[redacted]	[redacted]

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Niflumic acid	[redacted]	[redacted]	[redacted]
Nimeslide	[redacted]	[redacted]	[redacted]
Oxaprozin	[redacted]	[redacted]	[redacted]
Parecoxib sodium	[redacted]	[redacted]	[redacted]
Pelubiprofen	[redacted]	[redacted]	[redacted]
Phenylbutazone	[redacted]	[redacted]	[redacted]
Phenylbutazone; prednisolone	[redacted]	[redacted]	[redacted]
Piroxicam	[redacted]	[redacted]	[redacted]
Piroxicam betadex	[redacted]	[redacted]	[redacted]
Rofecoxib	[redacted]	[redacted]	[redacted]
Sulindac	[redacted]	[redacted]	[redacted]
Tenoxicam	[redacted]	[redacted]	[redacted]
Tiaprofenic acid	[redacted]	[redacted]	[redacted]
csDMARDs			
Any prior csDMARD	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]
Gold	[redacted]	[redacted]	[redacted]
Hydroxychloroquine	[redacted]	[redacted]	[redacted]
Hydroxychloroquine sulfate	[redacted]	[redacted]	[redacted]
Leflunomide	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Methotrexate sodium	[redacted]	[redacted]	[redacted]
Sulfasalazine	[redacted]	[redacted]	[redacted]
Thalidomide	[redacted]	[redacted]	[redacted]
Tripterygium wilfordii glycoside extract	[redacted]	[redacted]	[redacted]
Corticosteroids			
Any prior corticosteroids	[redacted]	[redacted]	[redacted]
Meprednisone	[redacted]	[redacted]	[redacted]
Methylprednisolone	[redacted]	[redacted]	[redacted]
Methylprednisolone acetate	[redacted]	[redacted]	[redacted]
Phenylbutazone; prednisolone	[redacted]	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]

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A12. In the CSR for study M16-098 the "Tables, Figures and Graphs Referred to but Not Included in the Text" section is blank (p135). This report is also referred to as being 'interim' (in the header). Please provide an updated version of the CSR with the missing tables, figures and graphs.

An updated version is provided as a separate document.

A13. Table 9 in the CSR for SELECT-AXIS1 reports the number of patients at baseline with psoriasis, inflammatory bowel disease and anterior uveitis. For both SELECT-AXIS1 and SELECT-AXIS2 please provide these data at randomisation and at 14-week follow-up.

The number and proportion of patients with psoriasis, inflammatory bowel disease and anterior uveitis at baseline for the SELECT-AXIS1 and SELECT-AXIS2 trials is presented in Table 10. As per the study protocols, this data was only collected at randomisation, as is common practice for trials in AS. It was observed that during the SELECT-AXIS1 study, no patient developed new onset uveitis, and events were observed only in patients with a history of uveitis. Over 64 weeks, the rate of uveitis was 5.5/100 PY. This includes 13 events in 8 patients; all were non-serious and assessed as having no reasonable possibility to be related to study drug. All cases of uveitis occurred in AS patients with a history of uveitis, were mild or moderate in severity, transient, and resolved with local treatment (corticosteroid eye drop).[32] Adverse events of IBD, ulcerative colitis, and Crohn's disease were not reported through one year of the OLE interim analysis, which included 182 patients with 237.6 PYs of exposure to upadacitinib (Date on file, UPA AS ISS; Deodhar 2020). Only 4 patients had a history of IBD (2 in each group) at baseline in SELECT-AXIS 1. 1 subject on placebo, who did not have a history of IBD, had a new onset. However, no new onset or exacerbation of IBD was observed in the upadacitinib arm over 64 weeks. A key exclusion criterion in the clinical trials was patients with extra-articular manifestations that are not clinically stable for at least 30 days prior to study entry.

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Table 10. Incidence of psoriasis, inflammatory bowel disease and anterior uveitis at randomisation the SELECT-AXIS1 and SELECT-AXIS2 trials

		Psoriasis n (%)	Inflammatory bowel disease n (%)	Anterior uveitis n (%)
SELECT-AXIS1				
Randomisation	Total	[redacted]	[redacted]	[redacted]
	Upadacitinib	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
SELECT-AXIS2				
Randomisation	Total	[redacted]	[redacted]	[redacted]
	Upadacitinib	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]

Indirect and mixed treatment comparisons – methods

A14. PRIORITY QUESTION: Please provide an electronic version of the R script, data input files and any other files required so that the NMA models can be re-run and checked by the ERG. This should include full details of the exact data used, number of iterations and models for each outcome and analysis.

This is provided in Appendix D.

A15. For some NMAs presented in Appendix D only a few studies are available per comparison (NMAs 4-5 for many outcomes only have 2 included studies). Thus, there is not enough information to reliably estimate the between-study heterogeneity (a minimum of 5 studies per comparison is recommended for adequate estimation – see Gelman, 2006[33]). This results in posterior distributions for the between-study sd that are not updated from the prior due to lack of data for some NMA models.

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

AbbVie does not believe that the included studies are likely to be heterogeneous and, as such, only FE models were presented in the main submission as the base case analysis. However, RE models were run for the purpose of completeness, and these have been included in the Appendix but should not be used for decision-making.

b) ***If there is* a priori *reason to believe that the included studies are likely to be heterogeneous but there is not enough information to reliably***

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estimate the heterogeneity, the use of informative prior distributions for the between-study heterogeneity may be justified (Dias et al 2018,[34] sections 2.3.2 and 6.3.2). Please present results using an appropriate empirically informed or minimally informative prior distribution for the random effects models for each outcome considered in the NMAs (Dias et al 2018,[34] sections 2.3.2 and 6.3.2; Röver et al 2021[35]).

AbbVie does not believe there is a priori reason to assume that the included studies for upadacitinib and ixekizumab are likely to be heterogenous. Therefore, we did not feel it is necessary to explore this question further and, instead, have focused on responding to those highlighted by the ERG as priority questions.

A16. PRIORITY QUESTION: The company fit a placebo-adjusted model to adjust for differences in the mean placebo effect across studies. For all outcomes for which an adjusted model was fitted, please also provide plots of odds ratios (for all comparators) against the odds of a response in the placebo arm (on the log-scale – see e.g. TSD3,[36] figure 7) so that the appropriateness of these adjustments can be assessed. Please also comment on which studies are contributing information to the estimation of the adjustment slope and how this should be interpreted.

As requested, please find below plots of relative treatment effects (e.g., odd ratios [ORs] for binary outcomes, relative changes from baseline [CFBs] for continuous outcomes) for all comparators versus the placebo effects (e.g., odds of a binary outcome and absolute CFBs of a continuous outcome) for each outcome to which an adjusted model was fitted. These plots are modelled on NICE DSU TSD3's Figure 7.[37] These outcomes include the binary outcomes: ASAS40 (Figure 3) and BASDAI50 (Figure 4***Figure 4***), as well as the continuous outcomes: BASDAI CFB (Figure 5

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Figure 5) and BASFI CFB (Figure 6*Figure 6*) in the bDMARD-naïve population.

In the bDMARD-IR population, fixed effects models are selected over random effects models. However, the placebo-adjusted fixed effects models did not converge and thus are not considered for selection. Hence, plots regarding bDMARD-IR population placebo-adjusted models are not presented here. Specific interpretations are noted below each figure.

All included studies in each network contributed information to the estimation of the adjustment slope. As such, mean treatment effects are centred on the mean placebo effect of the included studies. The adjustment utilises the assumption of a common regression term, in keeping with the example analyses presented in Section 4.4.1. of NICE DSU TSD3.[37] Dias et al. (2018), note that use of a common regression term is appropriate "[…] if the reference treatment is somehow different from the others, such as a placebo, an older treatment or 'standard care'."[38] As placebo serves as the common reference treatment in these analyses, use of a common regression term would accordingly be appropriate. While there may be appetite for treatment class-specific regression terms, this is likely to be unfeasible due to a paucity of data, particularly for the class of JAK inhibitors, with upadacitinib from SELECT-AXIS 1 providing the sole datapoint for three of the four outcomes fitted with an adjusted model. Indeed, as stated in NICE DSU TSD3,[37] the assumption of the common regression term "allows the interaction parameter to be estimated even for comparisons which only have one trial." Finally, akin to the analyses presented in Section 4.4.1. of NICE DSU TSD3,[37] the clear linear relationship between the treatment effect and the baseline risk shown for ASAS40 (Figure 3**Error! Not a valid bookmark self-reference.**) and BASDAI CFB (Figure 5

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Figure 5) (i.e., outcomes for which a placebo-adjusted model was selected) further lends support to the assumption of a common regression term.

Within the submission, the placebo-adjusted version of the selected fixed (FE) or random (RE) effects model was preferred if: 1) the model reached convergence criteria; 2) the 95% credible interval (CrI) of the adjustment regression coefficient (B) excluded 0; and 3) the median posterior between-study heterogeneity (sd) of a RE model decreased with the inclusion of the adjustment. These selection criteria are in line with the recommendation of NICE DSU TSD3[37] and Dias et al., 2018.[38] Within the submission, this ultimately led to the selection of the placebo-adjusted model in the bDMARD-naïve population for the ASAS40 and BASDAI CFB outcomes.

The same approach was adopted by the ERG during the MTA assessing TNFi for the treatment of AS.[22] Here, they concluded that a model with a RE variable capturing heterogeneity while allowing treatments to be similar, but not equal, was the best way to model available RCT data in AS. During the appraisal for secukinumab, the efficacy of secukinumab was found to be similar to TNFis and therefore, there has been no change in the efficacy of available treatments for AS with the introduction of secukinumab. In our case, the placebo effect could act as a proxy for capturing heterogeneity as observed during TA383.[22] During this appraisal, the model was used to demonstrate that TNFis have similar treatment effects, as observed with the NMAs presented in the company submission. Given the sparsity of data for AS, the results of the NMAs should be interpreted with caution. To accommodate any uncertainty, we have performed extensive sensitivity analysis, as presented in the company submission.

It should be noted that across the extensive sensitivity analysis (alternative time trial time points, random or fixed effects models, adjusted or unadjusted NMA, and additional variables), the results from the bDMARD-naïve and bDMARD-IR NMA revealed no significant differences between upadacitinib and comparators across key endpoints (ASAS40, BASDAI50, BASDAI CFB and BASFI CFB), demonstrating comparable treatment effects across all variables of interest. Based on these findings of similar effectiveness, AbbVie considers that upadacitinib fulfils the NICE criteria for a fast-track appraisal using a cost-comparison approach.

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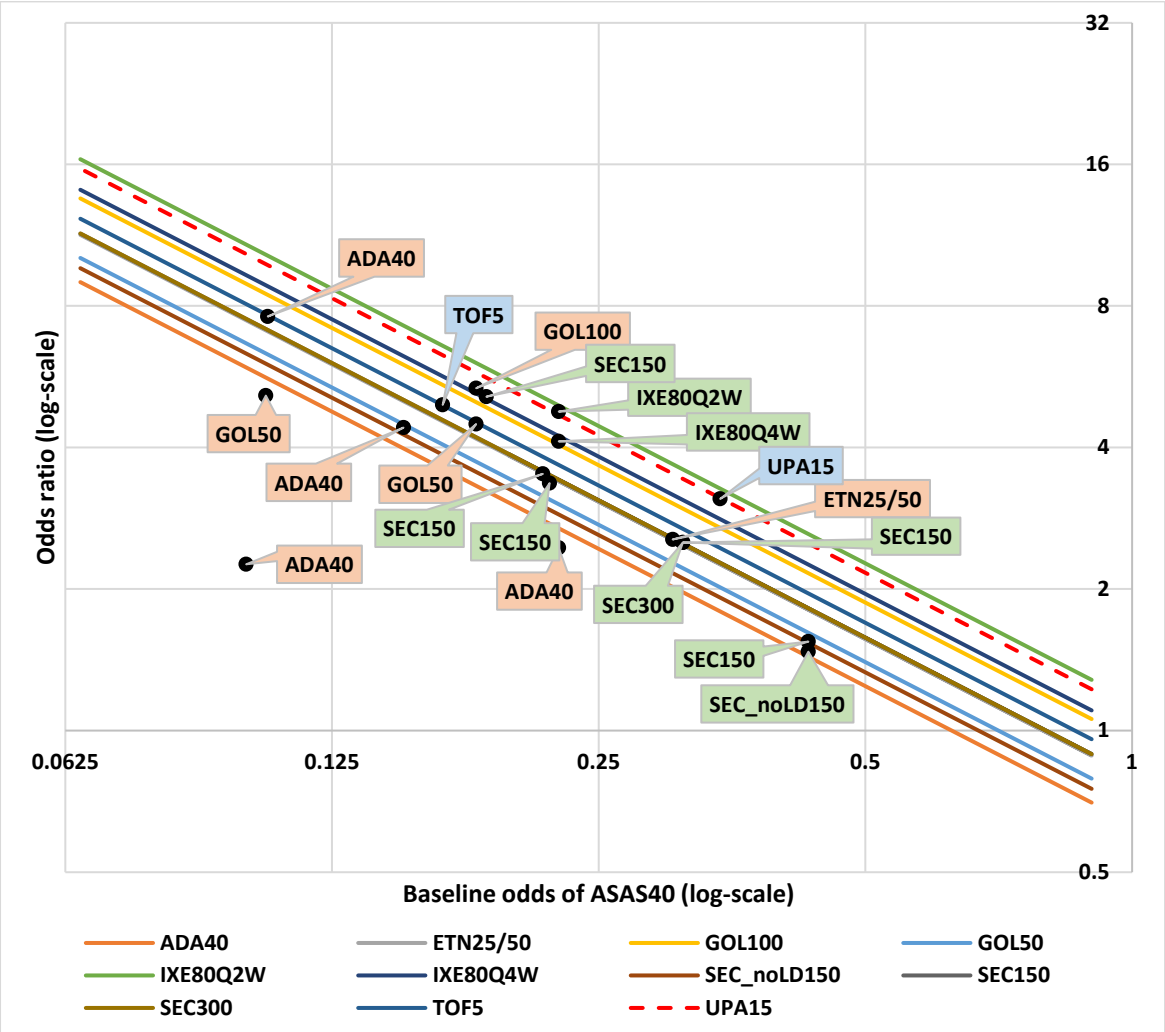
Figure 3. Baseline risk (placebo) adjustment for ASAS40 (bDMARD-naïve, Week 14 UPA, significant)



For the binary outcome ASAS40, the RE model with placebo adjustment (i.e., REA) was selected after meeting all three criteria (e.g., converged, B=-0.97 [95% CrI: -1.78 to -0.16], sd decreased from 0.35 to 0.2). The appropriateness of this adjustment is also reflected in Figure 3 above, where the datapoints show a strong linear relationship between the treatment effect and the baseline risk (on the log scale), and the parallel regression lines assuming a common interaction term fit nicely to the points. Of note, Figure 3 further supports a 'class placebo effect' for all treatments, as the relationship for anti-TNFs (orange-coloured callouts in figure), IL-17 inhibitors (green-coloured callouts in figure), and JAK inhibitors (blue-coloured callouts in figure) all appear to be consistent with the regression slope of -0.97, possibly except for an outlier datapoint for adalimumab (ADA40) from study M03-606 (baseline odds=0.1 and OR=2.26).

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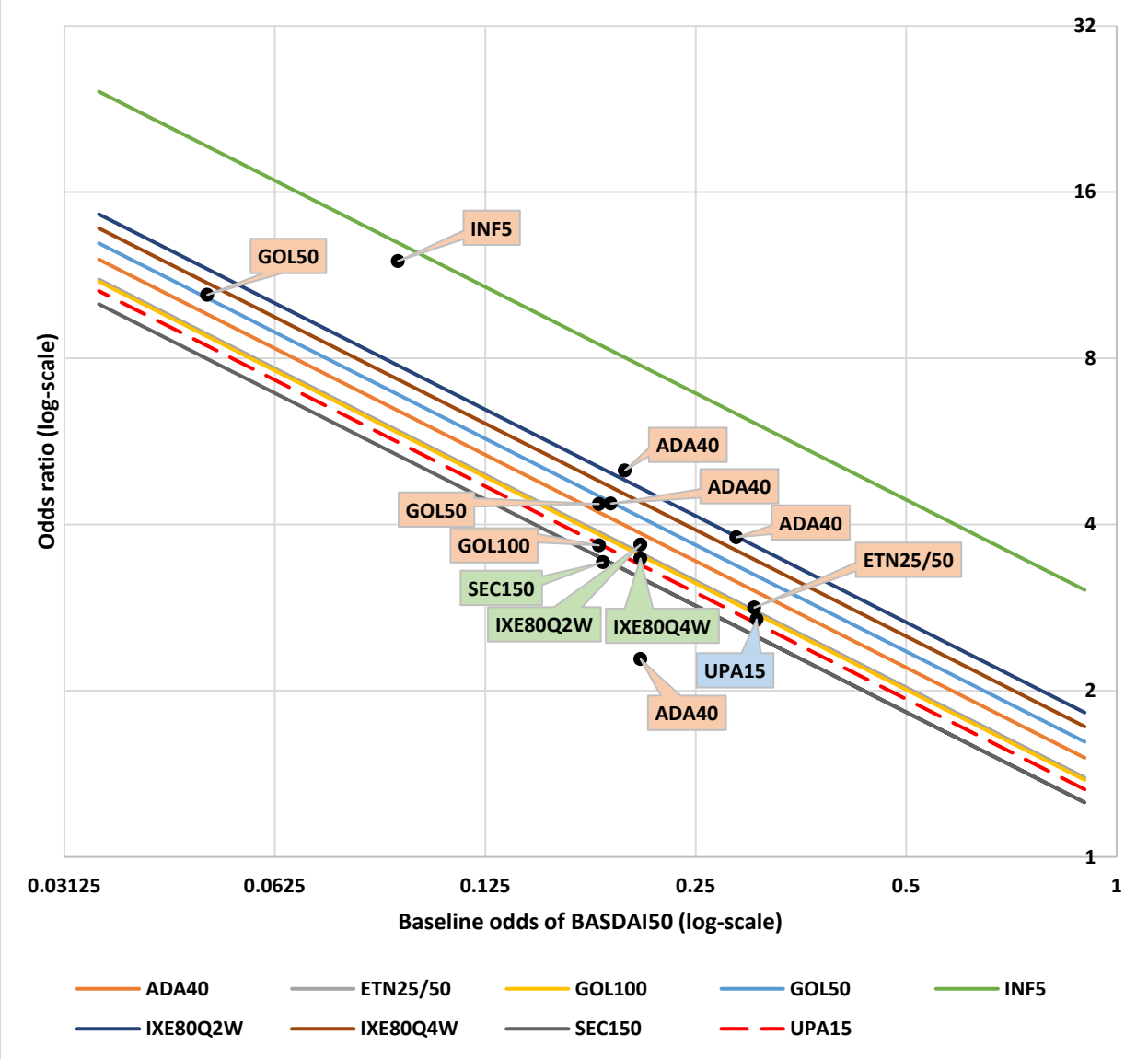
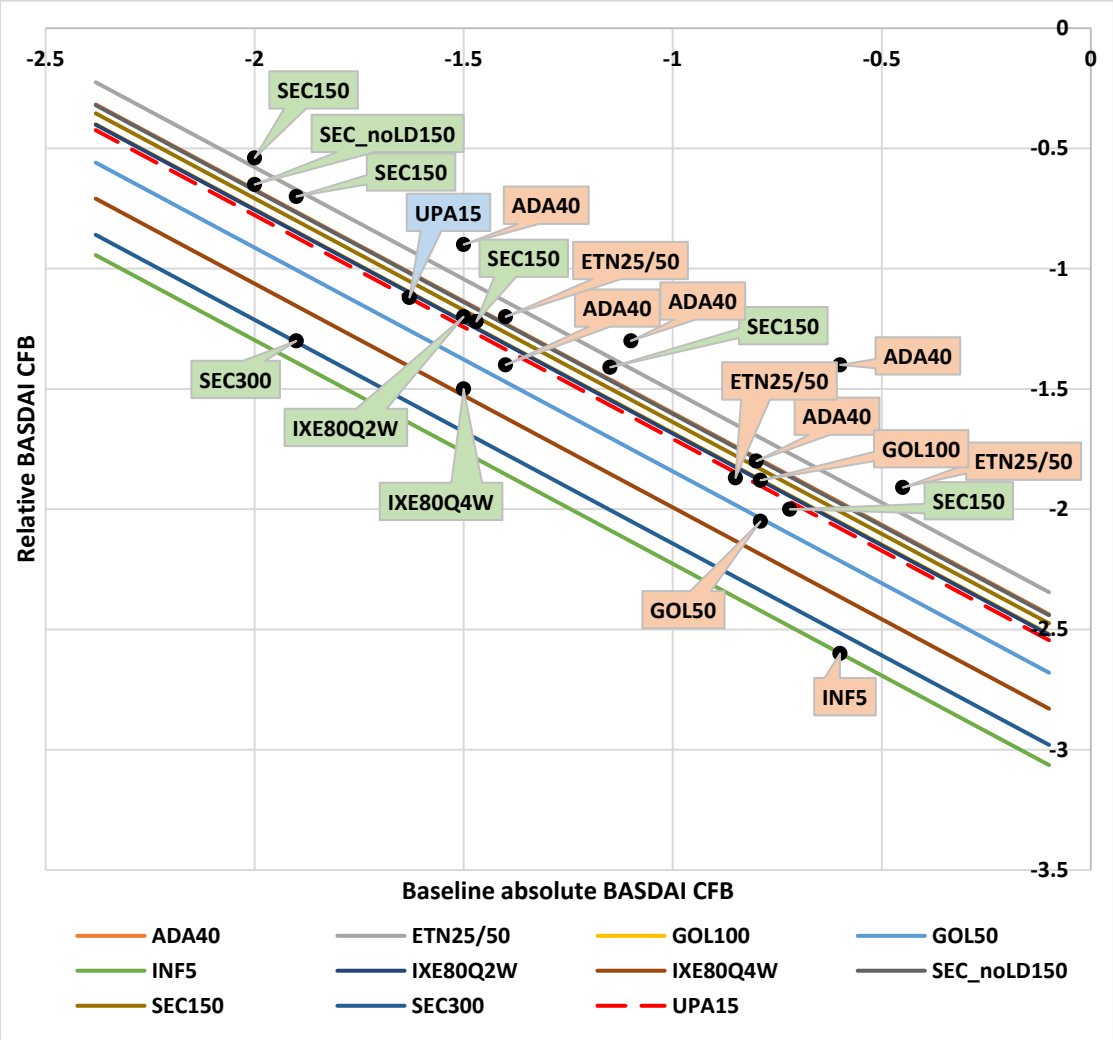
Figure 4. Baseline risk (placebo) adjustment for BASDAI50 (bDMARD-naïve, Week 14 UPA, not significant)



For the binary outcome BASDAI50, placebo adjustment on the RE model failed to meet the selection criteria (e.g., B=-0.64 [95% CrI: -2.78 to 1.56]). The insignificance of this adjustment is also reflected in Figure 4 above, where the datapoints are generally clustered around baseline odds of 0.2 to 0.3 and ORs of 3 to 5, with two outliers for infliximab (INF5; baseline odds=0.09 and OR=12) and golimumab (GOL50; baseline odds=0.05 and OR=10.4).

◊ Clarification questions

Figure 5. Baseline risk (placebo) adjustment for BASDAI CFB (bDMARD-naïve, Week 14 UPA, significant)



For the continuous outcome BASDAI CFB, the REA model was selected after meeting all three criteria (e.g., converged, B=-0.93 [95% CrI: -1.31 to -0.56], sd decreased from 0.38 to 0.09). The appropriateness of this adjustment is also reflected in Figure 5*Figure 4* above, where the datapoints show a strong linear relationship between the treatment effect and the baseline risk, and the parallel regression lines assuming a common interaction term fit nicely to the points. Similar to Figure 3All included studies in each network contributed information to the estimation of the adjustment slope. As such, mean treatment effects are centred on the mean placebo effect of the included studies. The adjustment utilises the assumption of a common regression term, in keeping with the example analyses presented in Section 4.4.1. of NICE DSU TSD3.[37] Dias et al. (2018), note that use of a common regression term is appropriate "[…] if the reference treatment is somehow different from the others, such as a placebo, an older treatment or 'standard care'."[38]

- Clarification questions

As placebo serves as the common reference treatment in these analyses, use of a common regression term would accordingly be appropriate. While there may be appetite for treatment class-specific regression terms, this is likely to be unfeasible due to a paucity of data, particularly for the class of JAK inhibitors, with upadacitinib from SELECT-AXIS 1 providing the sole datapoint for three of the four outcomes fitted with an adjusted model. Indeed, as stated in NICE DSU TSD3,[37] the assumption of the common regression term "allows the interaction parameter to be estimated even for comparisons which only have one trial." Finally, akin to the analyses presented in Section 4.4.1. of NICE DSU TSD3,[37] the clear linear relationship between the treatment effect and the baseline risk shown for ASAS40 (Figure 3**Error! Not a valid bookmark self-reference.**) and BASDAI CFB (Figure 5

- ◊ Clarification questions

Figure 5) (i.e., outcomes for which a placebo-adjusted model was selected) further lends support to the assumption of a common regression term.

Within the submission, the placebo-adjusted version of the selected fixed (FE) or random (RE) effects model was preferred if: 1) the model reached convergence criteria; 2) the 95% credible interval (CrI) of the adjustment regression coefficient (B) excluded 0; and 3) the median posterior between-study heterogeneity (sd) of a RE model decreased with the inclusion of the adjustment. These selection criteria are in line with the recommendation of NICE DSU TSD3[37] and Dias et al., 2018.[38] Within the submission, this ultimately led to the selection of the placebo-adjusted model in the bDMARD-naïve population for the ASAS40 and BASDAI CFB outcomes.

The same approach was adopted by the ERG during the MTA assessing TNFi for the treatment of AS.[22] Here, they concluded that a model with a RE variable capturing heterogeneity while allowing treatments to be similar, but not equal, was the best way to model available RCT data in AS. During the appraisal for secukinumab, the efficacy of secukinumab was found to be similar to TNFis and therefore, there has been no change in the efficacy of available treatments for AS with the introduction of secukinumab. In our case, the placebo effect could act as a proxy for capturing heterogeneity as observed during TA383.[22] During this appraisal, the model was used to demonstrate that TNFis have similar treatment effects, as observed with the NMAs presented in the company submission. Given the sparsity of data for AS, the results of the NMAs should be interpreted with caution. To accommodate any uncertainty, we have performed extensive sensitivity analysis, as presented in the company submission.

It should be noted that across the extensive sensitivity analysis (alternative time trial time points, random or fixed effects models, adjusted or unadjusted NMA, and additional variables), the results from the bDMARD-naïve and bDMARD-IR NMA revealed no significant differences between upadacitinib and comparators across key endpoints (ASAS40, BASDAI50, BASDAI CFB and BASFI CFB), demonstrating comparable treatment effects across all variables of interest. Based on these findings of similar effectiveness, AbbVie considers that upadacitinib fulfils the NICE criteria for a fast-track appraisal using a cost-comparison approach.

- ◊ Clarification questions

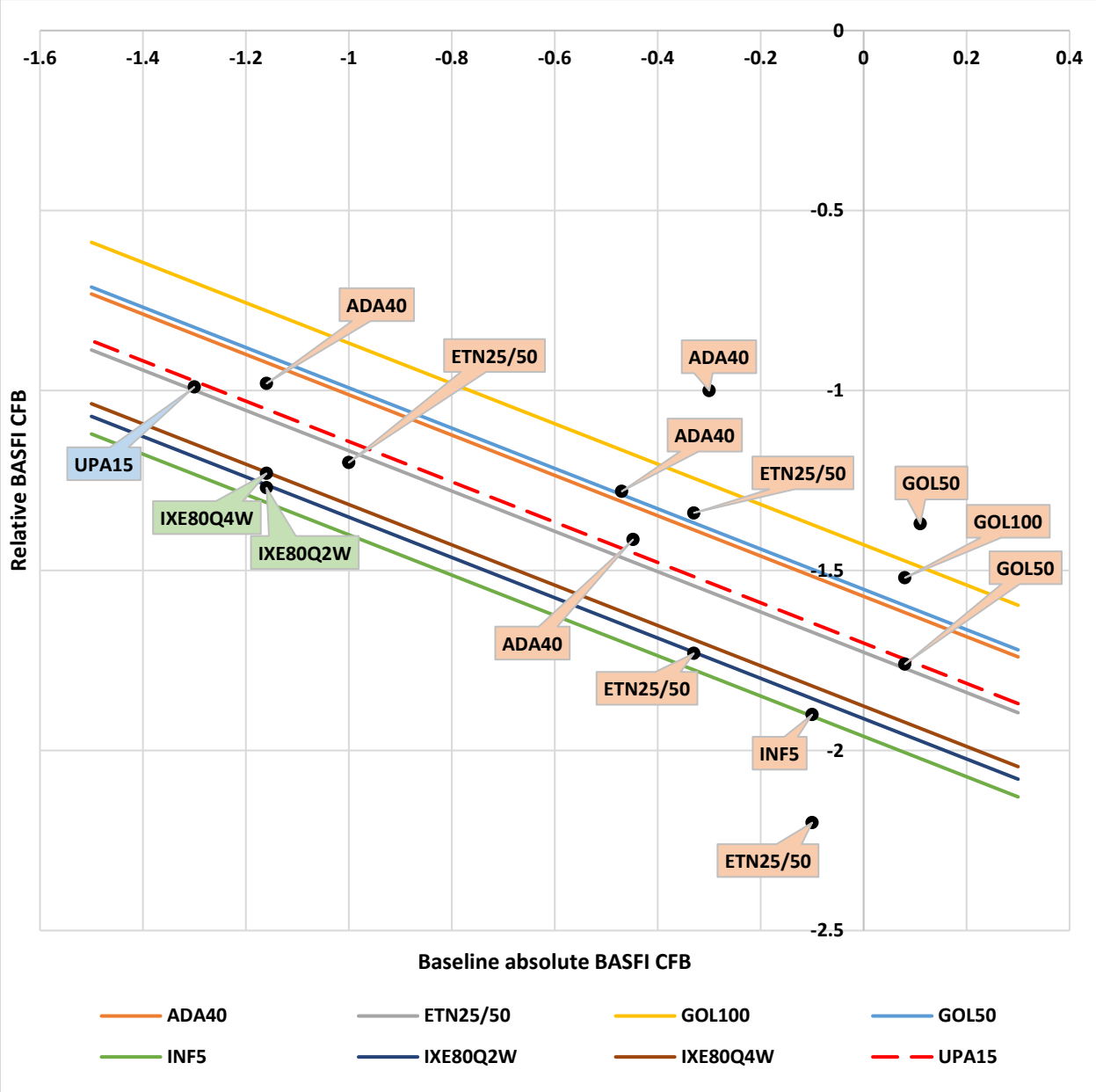
◊ Clarification questions

for ASAS40, Figure 5

- ◊ Clarification questions

Figure 5 further supports a 'class placebo effect' for all treatments, as the relationship for anti-TNFs (orange-coloured callouts in figure) and IL-17 inhibitors (green-coloured callouts in figure) both appear to be consistent with the regression slope of -0.93. Finally, note that for the JAK inhibitor UPA (blue-coloured callout in figure) any view on class-specific relationship should be taken with considerable caution since there is one datapoint and further evidence is needed to comment appropriately.

Figure 6. Baseline-risk (placebo) adjustment for BASFI CFB (bDMARD-naïve, Week 14 UPA, not significant)



For the continuous outcome BASFI CFB, placebo adjustment on the RE model failed to meet the selection criteria (e.g., B=-0.56 [95% CrI: -1.3 to 0.33]). The

- Clarification questions

insignificance of this adjustment is also reflected in Figure 6 above, where although the datapoints varied in baseline absolute BASFI CFB, the corresponding variations in relative BASFI CFB do not suggest a strong, clear relationship.

A17. For the ASASPR outcome, the baseline risks (μ's) were modelled as exchangeable across all 15 included studies to account for the zero events in the placebo arms of SELECT-AXIS 1. However, inspection of the baseline risks presented in sub-appendix B to Appendix D, shows these to be very different across studies which makes the exchangeability assumption questionable. Although the exchangeable baselines approach is one of the possible approaches to deal with this problem, it breaks randomisation across all studies by shrinking all placebo arms towards a common mean baseline risk, a problem which is exacerbated when baseline risks differ markedly across studies. Please repeat the NMAs for this outcome by applying a continuity correction to the SELECT-AXIS 1 study (add 0.5 to numerators and 1 to denominators). If there are still convergence problems, consider a frequentist NMA for this outcome (e.g. in R using 'netmeta').

It has not been feasible to conduct this analysis within the current time frame. However, ASASPR has not been considered by NICE to be a key outcome in the treatment of AS in previous technology appraisals. Additionally, across multiple key endpoints (ASAS40, BASDAI50, BASDAI CFB and BASFI CFB) and extensive sensitivity analysis (alternative time trial time points, random or fixed effects models, adjusted or unadjusted NMA, and additional variables), the presented NMAs revealed no significant differences between upadacitinib and comparators. Hence, this additional analysis is unlikely to change the conclusions of the analysis or identify a significant benefit for any AS treatment.

A18. NMA model selection procedures: when DIC differences are small (less than 3 to 5 points) across different fitted models, common practice is to choose the simplest model as it is easier to interpret and the DIC suggests no evidence justifying the additional complexity (TSD2[39] an Dias et al 2018,[34] section 3.3). However, the company often justify choice of a more complex model (e.g. RE model or placebo-adjusted model) by stating there is "no significant decrease in DIC" (Appendix D, section 5.3, several instances).

- ◊ Clarification questions

Please provide a reasoning for this approach, noting in particular the points made in questions A15 and A16.

AbbVie would agree that the wording included in Appendix D could benefit from additional clarity. For instance, the sentence “Like Primary NMA 1, there was a slight improvement in fit going from FE to RE models: Dbar decreased to be closer to the number of data points. Since the DIC remained essentially the same, the RE model is selected. Baseline-risk adjustment also appears to be unnecessary due to insignificant B.” (page 72 of Appendix D). However, in order to avoid confusion, we condensed this information in the main body, Document B, where we explicitly described our choice of models. In this case, we explained that the Dbar decreased by more than 1 point to be closer to the number of data points when going from FE model to RE model, and, even though the DIC did not show significant decrease, we selected RE model. We provided Appendix D as a supplementary document containing graphs that justify this reasonable selection. We also provided details on the discarded model for transparency purposes.

A19. PRIORITY QUESTION: For all outcomes, please present the NMA results for each comparator intervention vs upadacitinib in the form of a forest plot including the relative effects estimates and CrIs for all the different NMA models considered presented as different lines (see for example Fig 4d in Oba et al 2018[40]).

Please find below, relative effect estimate forest plots with 95% CrIs of each comparator intervention versus upadacitinib for all outcomes presented in the company submission with results from FE, RE, placebo-adjusted FE (FEA), and placebo-adjusted RE (REA) models presented as different lines.

To improve readability, the lower and upper values of the forest plots have been bounded. For plots of ORs (binary outcomes), the upper bound is bounded at 20. For plots of relative CFBs (continuous outcomes), the lower and upper bounds are bounded at -10 and 10, respectively. Instances where the lower and/or upper bounds of a comparison fall outside the noted scale are mentioned for each plot.

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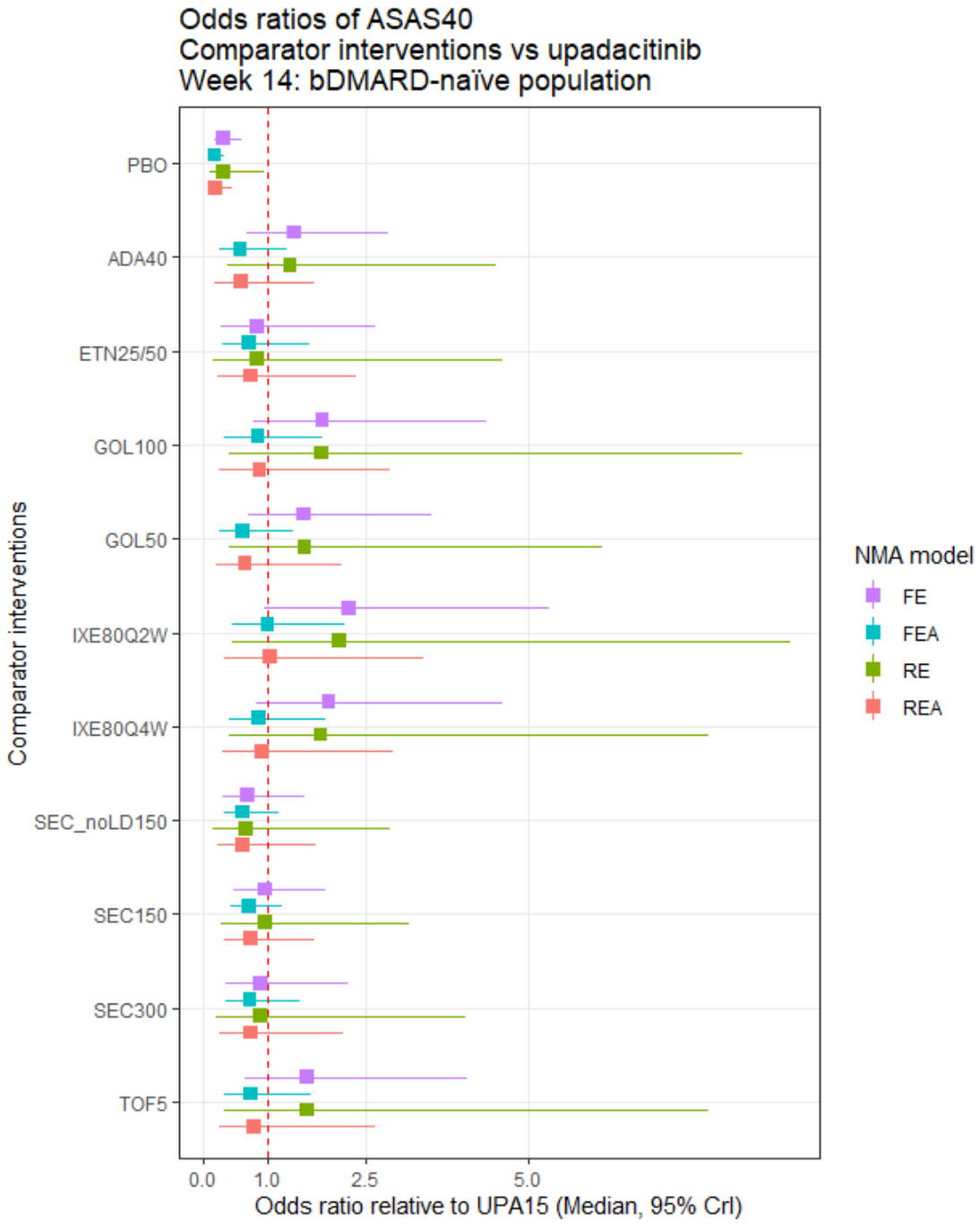
As these plots were constructed as a comparator intervention versus upadacitinib (i.e., upadacitinib serves as the reference treatment), for binary outcomes points to the left of the vertical (red dashed line) favour upadacitinib while points to the right of the line favour the comparator intervention; for continuous outcomes points to the right of the vertical (red dashed line) favour upadacitinib while points to the left of the line favour the comparator intervention.

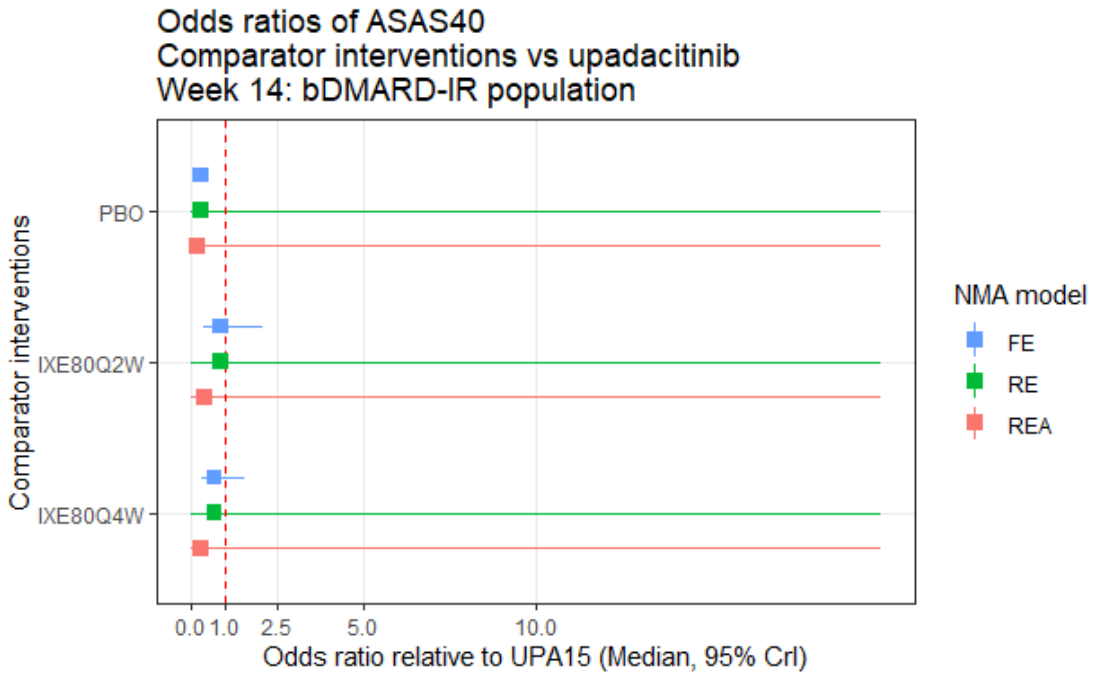
- Clarification questions

Figure 7. ASAS40 outcome, bDMARD-naïve population forest plot



◊ Clarification questions

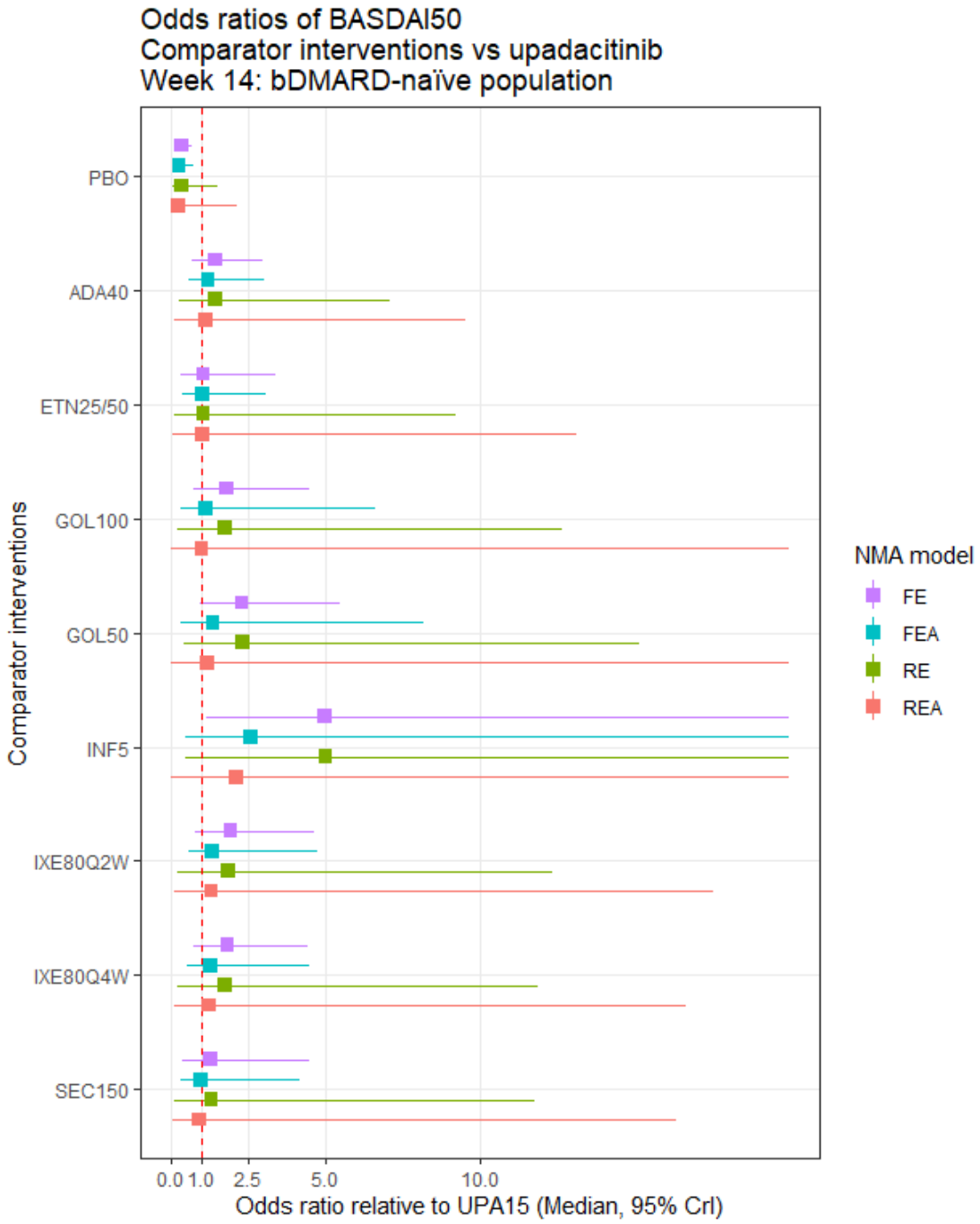
Figure 8. ASAS40 outcome, bDMARD-IR population forest plot



FEA model does not converge (results not displayed); RE and REA upper bounds are off plot scale.

◊ Clarification questions

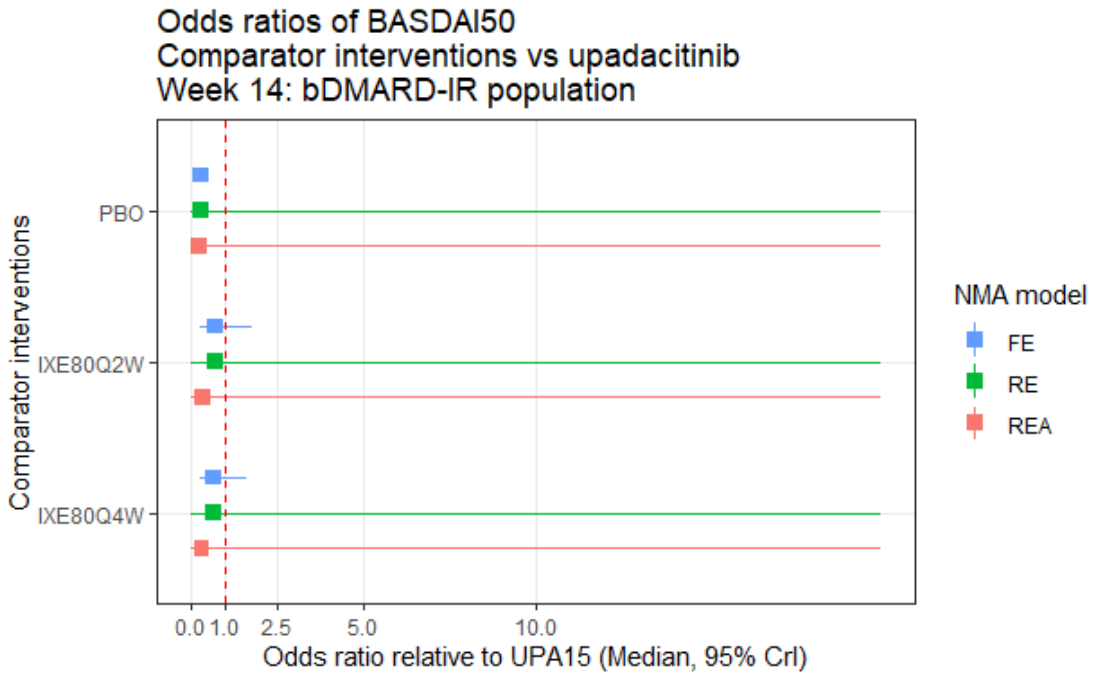
Figure 9. BASDAI50 outcome, bDMARD-naïve population forest plot



REA upper bounds are off graphic scale for some comparisons (GOL100, GOL50). All model upper bounds are off plot scale for the INF5 vs UPA15 comparison.

- Clarification questions

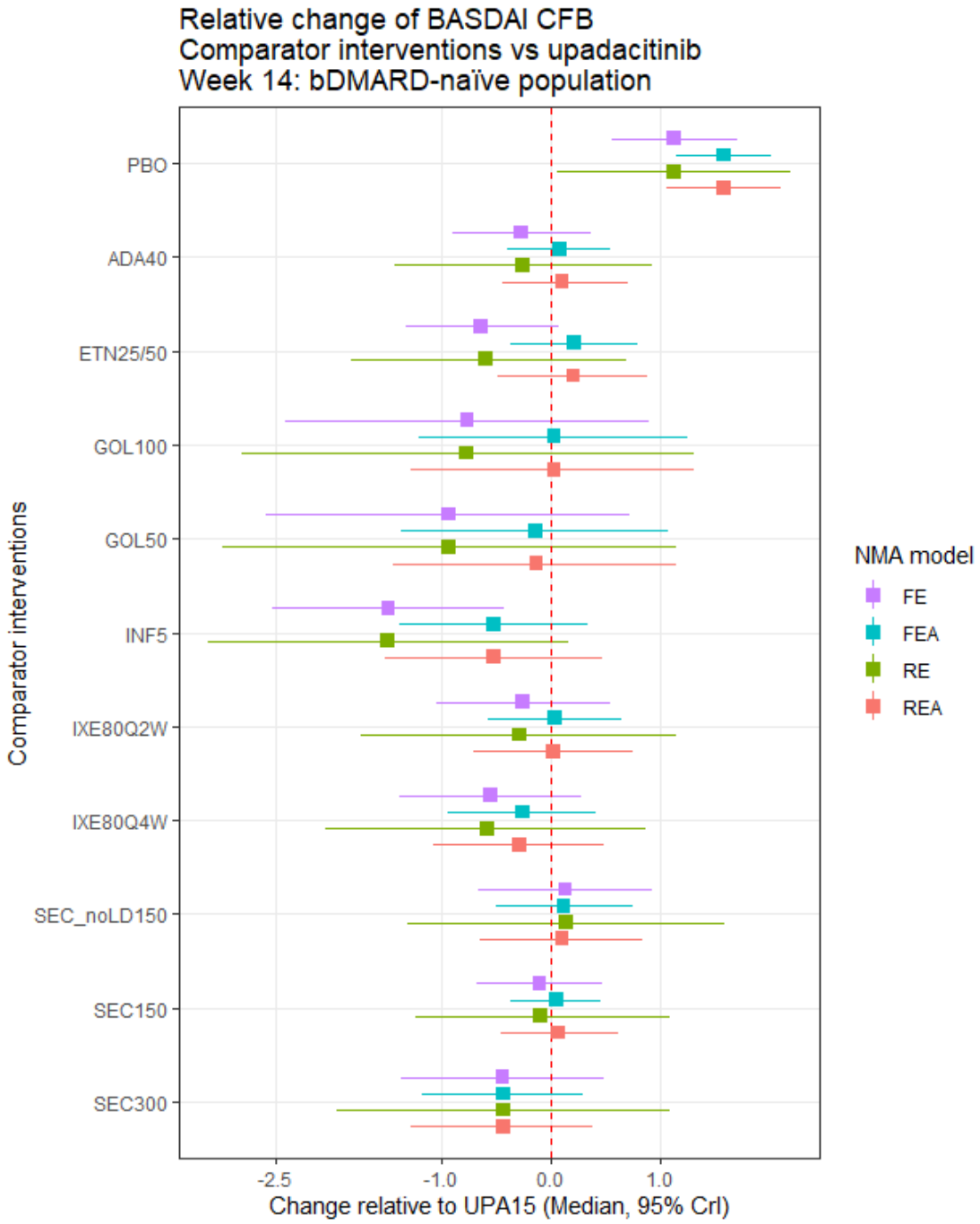
Figure 10. BASDAI50 outcome, bDMARD-IR population forest plot



FEA model does not converge (results not displayed); RE and REA upper bounds are off plot scale.

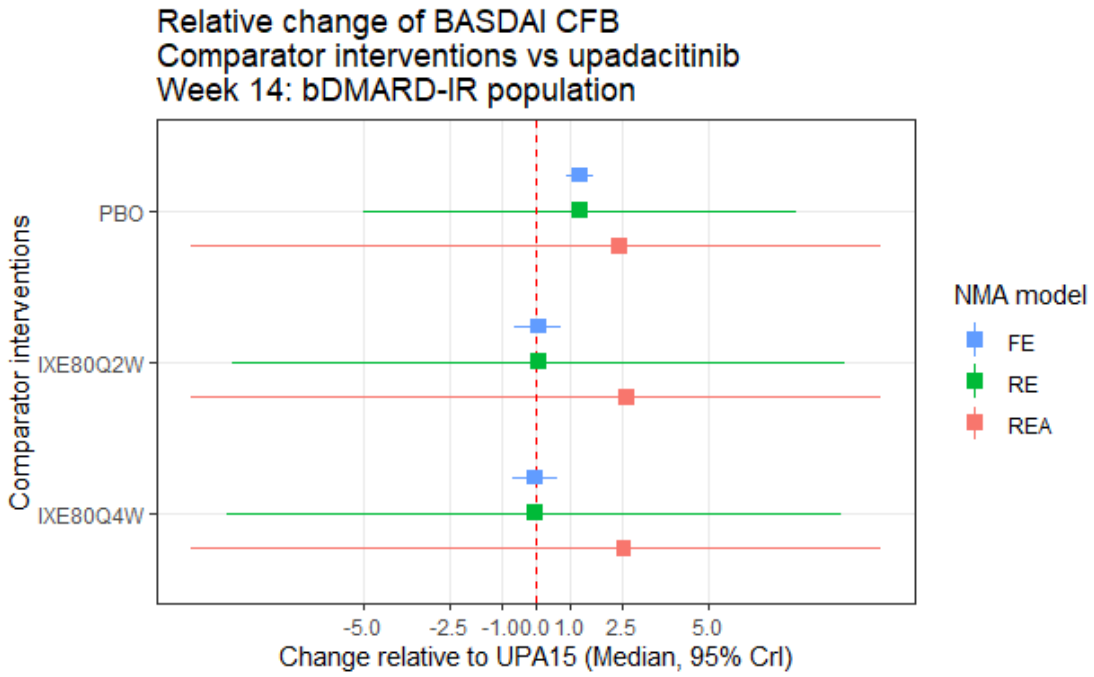
- Clarification questions

Figure 11. BASDAI CFB outcome, bDMARD-naïve population forest plot



◊ Clarification questions

Figure 12. BASDAI CFB outcome, bDMARD-IR population forest plot



FEA model does not converge (results not displayed); REA bounds are off plot scale.

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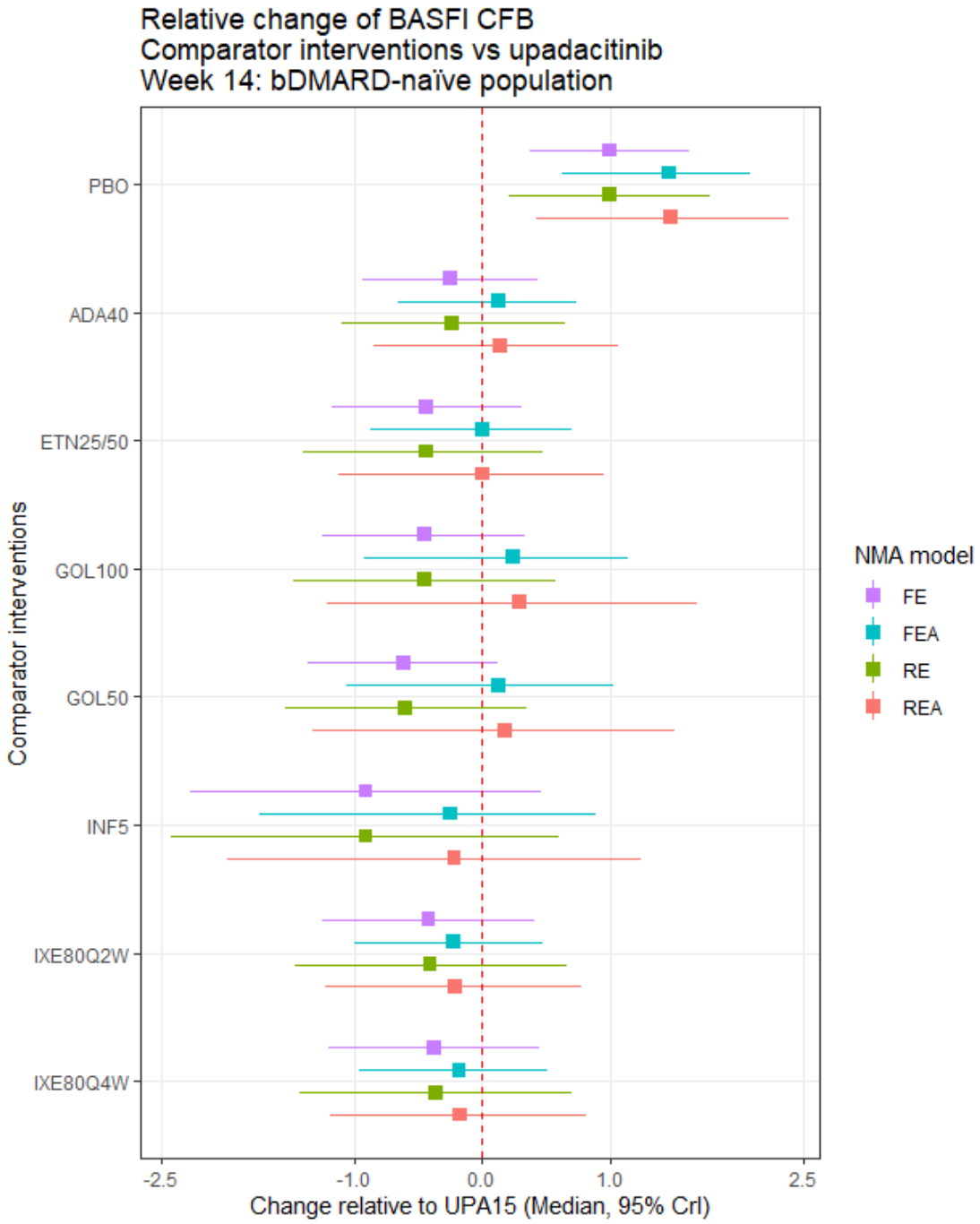
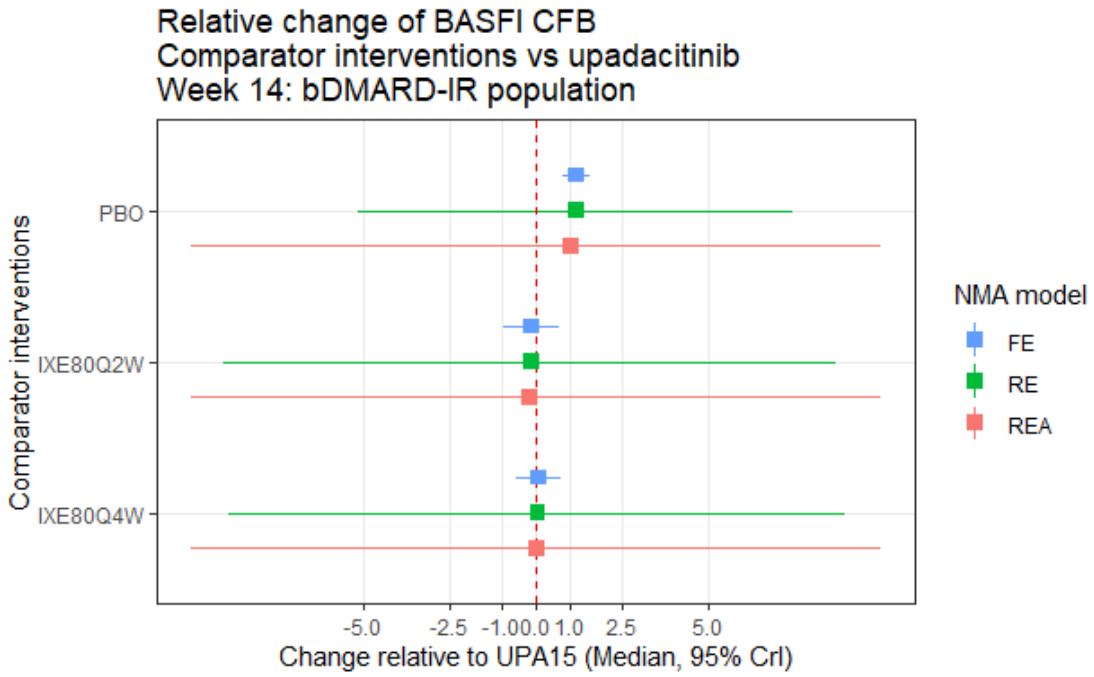
Figure 13. BASFI CFB outcome, bDMARD-naïve population forest plot



◊ Clarification questions

Figure 14. BASFI CFB outcome, bDMARD-IR population forest plot



FEA model does not converge (results not shown); REA bounds are off graphic scale.

Indirect and mixed treatment comparisons – data

A20. PRIORITY QUESTION: Table 8 in Appendix D details the selected models for NMAs 1 to 5 for 7 outcomes. However, for ASAS20, ASASPR and Total back pain, no network plots, network characteristics (Tables 75, 77, 81), model selection plots (section 5.3) or results are presented (section 5.4). Please provide these details.

Currently available outcomes are presented in Appendix D. It has not been feasible to conduct further analysis within the current time frame. However, as noted in response to Question A17, ASAS20, ASASPR and total back pain are not considered by NICE to be key outcomes in the treatment of AS in previous appraisals. The NMAs focused on providing evidence for key outcomes of interest (ASAS40, BASDAI50, BASDAI CFB and BASFI CFB) and identified no significant differences between upadacitinib and comparators.

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A21. In Section 4.4.2 of Appendix D, the company describe 5 NMA models based on patients' previous bDMARD experience. Please provide details of the exact data included in each NMA.

AbbVie would like to reiterate that for transparency purposes we provided Appendix D, which included a broad range of analysis. This was provided in the spirit of transparency, however not all analyses were deemed directly relevant to the NICE submission and therefore not referenced or included in the main submission document. The base case analysis presented in the main submission document includes networks that do not pool data based on patients' previous bDMARD experience. We believed that our approach was reasonable given results from two NMAs directly relevant to the defined decision problem (bDMARD-naïve and bDMARD-IR patients). These findings are further supported by a comprehensive, robust, and wide range of additional analyses which presented results using alternative time trial time points, random or fixed effects models, adjusted or unadjusted NMA, and additional variables tested.

Section B: Clarification on cost-effectiveness data

Adverse events costs

B1. PRIORITY QUESTION: Please consider the expected implications of the monitoring, prevention (e.g., statins, use of compression devices, etc.) and of the management and treatment of: i) relevant shorter-term adverse events identified in the clinical trial (justify inclusions and exclusions in the updated cost-comparison requested in question B2), and ii) long-term adverse events identified in questions A6.

Clinical feedback indicates that monitoring for the use of all JAKi in patients with immune-mediated inflammatory diseases is similar to all advanced therapies. The only difference for JAKi is lipid monitoring, which is the same as currently available IL-6 therapies.

Rheumatoid arthritis and autoimmune conditions patients have an increased risk for cardiovascular (CV) disorders. Patients treated with any therapy should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of

care which is usually part of primary care assessment, regardless of treatment type. None of the monitoring is additional for the NHS and sits in routine care and with primary care. Height, weight and blood pressure are taken routinely for all patients not just patients with autoimmune conditions.

As noted previously, impactful adverse events are very infrequent when receiving upadacitinib, as outlined in Table 3 and Table 4. The incidence of serious adverse events for upadacitinib at week 104 was 5.9 per 100 patient-years during SELECT-AXIS1, which is broadly in line with that observed for comparators (4.8–9.4 per 100 patient-years). As a result, even when an adverse event is costly, there is a minimal impact on cost-effectiveness. Given this small impact, an additional scenario analysis is provided to assess the inclusion of additional monitoring and prevention costs for adverse events, reflecting the response to Question B2.

Results of this scenario analysis build on the updated base case analysis defined in response to question B6 (as opposed to the original base case analysis).

Feedback from clinical experts suggests that monitoring protocols may differ between centres treating AS patients receiving JAK inhibitors (i.e., upadacitinib) and Il-17 inhibitors (i.e., secukinumab and ixekizumab). One particular protocol AbbVie were able to source from a clinical expert during the ERG clarification question stage indicates additional frequency of monitoring is applied for patients receiving jak inhibitors compared to IL17 therapies in the first 3 month period. However, this did not include additional types of tests. Costs associated with the additional frequency are described in Table 11; cells highlighted in blue represent monitoring frequencies and/or costs that differ from those applied in the base case analysis.

It should be noted that the monitoring and assessment costs already captured in the base case analysis encompass the majority of monitoring and assessment procedures that are expected to be undertaken alongside standard of care, and that these have been validated by clinician feedback in multiple health technology assessments.

- ◊ Clarification questions

Results of this scenario analysis are presented in Table 12 and demonstrate little impact on modelled results (when compared to updated base case results – see response to B6). Due to potential for variability across centres and the accepted approach in previous appraisals, this remains a scenario analysis rather than a formal change to the base-case.

- Clarification questions

Table 11. Summary of treatment monitoring costs applied in scenario analysis

Monitoring component	Cost per component	Frequency of use (A)				Justification / Source
		Upadacitinib		Ixekizumab / Secukinumab		
		Initial 3 months	Subsequent 3-month periods	Initial 3 months	Subsequent 3-month periods	
Specialist visits	£125.44	2	0.5	2	0.5	TA407[41]; Emery et al. (2018)[42]; Corbett et al. (2016)[43]; NHS Reference Costs 2019/20 (WF01A - Total HRG)[44]
Full blood count	£2.56	3	1	2	1	TA407[41]; Emery et al. (2018)[42]; Corbett et al. (2016)[43]; NHS Reference Costs 2019/20 (DAPS05 - Total Other Currencies)[44]
Erythrocyte sedimentation rate	£2.56	2	1	2	1	
Liver function test	£1.20	3	1	2	1	TA407[41]; Emery et al. (2018)[42]; Corbett et al. (2016)[43]; NHS Reference Costs 2019/20 (DAPS04 - Total Other Currencies)[44]
Urea and electrolytes test	£1.20	3	1	2	1	
Chest radiograph	£27.14	1	0	1	0	TA407[41]; Emery et al. (2018)[42]; Corbett et al. (2016)[43]; NHS Reference Costs 2019/20 (WF01B - CL - Diagnostic Imaging - First Attendance)[44]
Interferon gamma release assay	£116.84	1	0	1	0	'Akubakar et al. 2018; PSSRU 2020
Antinuclear antibodies	£7.35	1	0	1	0	TA407[41]; Emery et al. (2018)[42]; Corbett et al. (2016)[43]; NHS Reference Costs 2019/20 (DAPS06 - Total Other Currencies)[44]
DNA double-strand test	£7.35	1	0	1	0	
Albumin monitoring	£2.56	3	1	1	1	NHS Reference Costs 2019/20 (DAPS05 - Total Other Currencies)[44]
Lipid profile monitoring	£2.56	1	1	0	0	NHS Reference Costs 2019/20 (DAPS05 - Total Other Currencies)[44]

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

Notes

Cells highlighted in blue represent monitoring costs that differ from those applied in the base case analysis.

A: Monitoring costs are applied to all patients receiving treatment

B: Cost could not be sourced from contemporary literature and so the cost used in TA383 was inflated to 2020 costs using the 2020 PSSRU NHSCII pay and prices indices.

Table 12. Scenario analysis results: Impact of additional monitoring and assessment costs

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Proportion remaining on treatment at 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	£16,494	£12,798	£11,390	£10,137	£9,022	£59,840
Secukinumab	£10,209	£6,522	£5,804	£5,166	£4,598	£32,299
Incremental undiscounted costs (A)						
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

B2. PRIORITY QUESTION: For relevant short-term adverse events identified in the clinical trial and for each of the long-term adverse events identified in question A6 consider the following:

a) Comment on the likelihood of the occurrence of these events, with and without treatment with upadacitinib, in both the overall population (as per the marketing authorisation) and in a population restricted to patients over 65 years of age, current or past smokers, or individuals with other cardiovascular (such as diabetes or coronary artery disease) or malignancy risk factors (in line with current restrictions by the MHRA for tofacitinib[11]).

The clinical data for upadacitinib does not reveal increased risks of MACE, thrombosis, malignancy (excluding NMSC), or mortality and therefore the upadacitinib SmPC sections regarding MACE, malignancy and thrombosis are unchanged.

After up to 2 years of follow-up, there were no serious infections, NMSC, MACEs or VTEs reported in the SELECT-AXIS 1 trial (Table 4). In SELECT-AXIS 1, the proportion of patients with AEs was generally similar in the upadacitinib and placebo

groups. No serious infections, malignancies, anaemia, lymphopenia, herpes zoster, renal dysfunction, adjudicated major adverse cardiovascular events, venous thromboembolic events, or deaths were reported, and haemoglobin levels remained consistent throughout the first 14 weeks of the study.[16] No new safety findings, no serious infections, active tuberculosis, adjudicated MACE, lymphoma, non-melanoma skin cancer, renal dysfunction, or gastrointestinal perforations were observed over 2 years.

Concern for an increased risk of MACE with JAK inhibitor therapy was initially raised due to changes in lipid levels, including rises in low-density lipoprotein-cholesterol (LDL-C). Other RA therapies that reduce the inflammatory response like TNFi have also been associated with smaller rises in LDL-C. Similar to other JAKi, upadacitinib results in increased LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglyceride levels; although atherogenic indices based on ratios of total cholesterol/HDL C, LDL C/HDL-C, and ApoB/ApoA1 ratios remained unchanged. Therefore, we would not expect the rate of MACE to be any higher in patients treated with upadacitinib.

The safety profile of upadacitinib was aligned to that of the IL-17A inhibitors, secukinumab and ixekizumab both during the short-term and longer-term follow-up (**Error! Reference source not found.** and **Error! Reference source not found.**, respectively), and therefore, we do not expect the occurrence of short-term and long-term AEs to be greater in patients treated with upadacitinib compared to patients treated with IL-17A inhibitors.

b) In the cost-comparison model, please include the costs of any additional baseline risk assessments that may be implemented in clinical practice (such as cardiovascular risk assessment, i.e. QRISK3) prior to initiating treatment with upadacitinib. For cardiovascular risk, this should at least

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include lipid profiling, blood pressure measurement, body weight measurement, and diabetes tests.

c) ***In the cost-comparison model, please include the likelihood and costs of additional routine monitoring for patients on treatment that may be implemented in clinical practice, such as annual lipid profile monitoring.***

d) ***In the cost-comparison model, please include the likelihood and costs of further preventative actions, such as treatment with statins for patients experiencing elevated lipid levels.***

e) ***In the cost-comparison model, please include the likelihood of occurrence of adverse events, the costs of their diagnosis and of their management and treatment (e.g. low molecular weight heparin, warfarin for venous thromboembolic disease).***

As noted in response to Question B1, impactful adverse events are very infrequent when receiving upadacitinib, so that even if costly, there is a minimal impact on cost-effectiveness. Given this small impact, the response to Question B1 includes an additional scenario analysis with the inclusion of additional monitoring and other risk assessments.

Results of the scenario analysis are presented in Table 12 and demonstrate little impact on modelled results.

B3. The new restrictions imposed by the MHRA may lead to patients being treated with upadacitinib having to permanently discontinue treatment if they develop risk factors for venous thromboembolism, MACE, or malignancy. Based on your understanding of the prevalence of these risk factors in the NHS AS population (and their relationship with increasing age), what effect might this have on discontinuation rates relative to the comparator treatments.

Upadacitinib's clinical data does not reveal increased risks of MACE, thrombosis, malignancy (excluding NMSC), or mortality and therefore the upadacitinib SmPC sections regarding MACE, malignancy and thrombosis are unchanged. In addition, restriction for other JAK inhibitors and other patient populations do not apply to this AS patient population. Clinicians advise that in terms of rheumatology, AS patients

are on average younger and tend to have fewer comorbidities and risk factors; therefore, after considering the benefit and risk for the individual patient prior to initiating therapy, they do not foresee any reason to discontinue therapy related to developing venous thromboembolism, MACE, or malignancy. As with all patients the risk assessment would be done before initiating any therapy. Following standard clinical practice, all health care professionals would follow local guidance, EULAR and BSR guidelines and recommendations on the SmPC. For all rheumatology patients, the clinician would take a history and assess any risk factors prior to starting any therapy. Risk factors that should be considered in determining the patient's risk for DVT/PE include older age, obesity, a medical history of DVT/PE, patients undergoing major surgery and prolonged immobilisation. Overall, this would not affect discontinuation rates as the patients are very unlikely to be taking any JAKi if they have been identified as having risk factors.

B4. Clinical advisors to the ERG indicate that adherence to daily oral treatment is likely to be an important issue in clinical practice for upadacitinib, particularly in relation to alternative treatments which are delivered by monthly injection. Please comment on how this could affect treatment effectiveness and patient outcomes for example if doses are missed.

There is no evidence to support reduced adherence as a result of switching to daily oral treatment, as there would be not evidence to support improved adherence as a result of switching to monthly injections. There are adherence risks and benefits associated with all modes of administration. Patients may be more adherent to oral therapies than alternative treatments as a result of poor technique when self-administering monthly injections. Additionally, patients may prefer oral therapies due to mobility problems, reducing their ability to attend injection appointments or self-administer therapies. Further, patients who self-administer may not administer injections at home at a similar rate to patients taking oral tablets.

When patients with axSpA, including those with AS, were specifically asked about their preferences regarding treatment administration, 90% chose to receive their medication at home and 78.6% preferred a treatment they could administer themselves.[46] Similarly, 51.4% of axSpA patients in this study would prefer an oral treatment.[46] This demonstrates a clear patient desire for a more convenient oral

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treatment option in AS, where patients have greater autonomy over their own care and can adapt their treatment around their current lifestyles.

The BSR and BHPR guidelines for the treatment of axial spondyloarthritis, including AS, highlight the importance of patient choice when considering treatment.[47] This choice should also include how patients receive their treatment as they are more likely to be motivated by the modality they chose.[48]

The availability of an oral mode of administration in a disease with limited alternatives outweighs the potential risks of non-adherence and provides an opportunity for AS patients to optimise their treatment adherence according to their preferences.

Drug acquisition and administration

B5. Clinical advisors to the ERG indicate that most patients will have received training in the use of self-injecting subcutaneous biologics at previous lines of treatment and are unlikely to require re-training. Moreover, some companies provide self-injection training free of cost. Can the company provide evidence of whether such training is being provided in the NHS at either first or subsequent lines of treatment?

It is acknowledged that there is some uncertainty around the cost of self-injection training and when it may occur. As ixekizumab may only be administered after prior biologic therapy, patients receiving this therapy may have previously received prior self-injection training and retraining may not be required. However, secukinumab may be administered in biologic naïve patients, and so will require this training. Further, it is unclear the proportion of patients who would receive this training free of cost.

To address this uncertainty and assess the impact, a conservative scenario analysis has been provided in which training for self-injecting subcutaneous biologics is assumed to have already taken place or the training is free of cost to the NHS. This scenario builds on the updated base case analysis results presented in response to Question B6.

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Results of the scenario analysis are presented in Table 13 and demonstrate little impact on modelled results (when compared to updated base case results presented in Table 13 for comparison), reducing the cost savings to [redacted] for ixekizumab (from [redacted]) and [redacted] for secukinumab (from [redacted]) in the first year.

Table 13. Scenario analysis results: Impact of no cost assumed for training for self-injecting subcutaneous biologics

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Scenario analysis: Total undiscounted costs						
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	£16,436	£12,789	£11,382	£10,130	£9,016	£59,753
Secukinumab	£10,151	£6,513	£5,797	£5,159	£4,592	£32,212
Scenario analysis: Incremental undiscounted costs (A)						
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated base case analysis: Incremental undiscounted costs (A) – see Table 14						
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

B6. Please check the dosing frequency of ixekizumab in Months 1-3 in the cost-comparison analysis. The ERG calculate that 5 doses would be used in Months 1-3, which would on average comprise 13.04 weeks (2 loading doses at week 0, doses at weeks 4, 8, and 12, for a likely total of 5 doses). Please adjust the cost-comparison analysis if appropriate.

The dosing frequency has been amended. As other amendments have been made to the base case cost-comparison analysis (in response to questions B6, B7, C4 and C6), we have provided results in Table 14 below that encompass all of these changes. These updates can be considered the new base case analysis.

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Table 14. Updated base case cost comparison results

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Proportion remaining on treatment at 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	£16,484	£12,789	£11,382	£10,130	£9,016	£59,801
Secukinumab	£10,199	£6,513	£5,797	£5,159	£4,592	£32,260
Incremental undiscounted costs (A)						
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Monitoring and other costs

B7. Clinical advice to the ERG suggests that the Tuberculosis Heaf test is no longer commonly used to detect latent TB, with the interferon gamma release assay (IGRA) typically used in patients prior to use of immunosuppressive treatments. Please update the monitoring costs to reflect current clinical practice regarding TB testing.

The cost of an IGRA could not be identified from NHS costing data and so data from a recent health technology assessment looking at gamma release assays for predicting active tuberculosis was used.[49] A cost of £112 was utilised in the analysis. This cost was assumed to represent 2017 costs and was inflated to 2020/21 costs using the PSSRU NHSCII cost inflation indices,[50] giving a final cost of £116.84.

As other amendments have been made to the base case cost-comparison analysis (in response to questions B6, B7, C4 and C6), please see the response to question B6 for updated results corresponding to all of these changes.

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Time horizon

B8. PRIORITY QUESTION: Please provide an updated version of the cost-comparison model, which allows consideration of alternative time horizons (with costs disaggregated by year). Include sensitivity analyses for a time horizon equal to mean treatment duration, and for time horizons of 2, 5 and 10 years.

Additional results have been provided detailing cost comparison results at the requested time horizons. Based on an exponential approximation, and using an annual discontinuation rate of 11%, the mean duration of treatment is estimated to be 9.09 years, therefore a time horizon of 10 years seems an implausible scenario. As a result, we have provided results at 9 years as an additional time horizon and kept this as scenario analysis only.

Although this scenario analysis includes comparator list prices only, AbbVie believes that the recommendation of upadacitinib still has the potential to offer cost-savings to the NHS and, at the very least, can address a high unmet need at a similar cost to currently recommended therapies.

Results of the analysis are presented in Table 15 and encompass the base analysis changes described in response to question B6.

Table 15. Updated base case cost comparison results (extended time horizon)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Total (2 years)	Total (5 years)	Total (9 years)	Total (10 years)
Proportion remaining on treatment at end of year														
Upadacitinib	89.00%	79.21%	70.50%	62.74%	55.84%	49.70%	44.23%	39.37%	35.04%	31.18%	-	-	-	-
Ixekizumab	89.00%	79.21%	70.50%	62.74%	55.84%	49.70%	44.23%	39.37%	35.04%	31.18%	-	-	-	-
Secukinumab	89.00%	79.21%	70.50%	62.74%	55.84%	49.70%	44.23%	39.37%	35.04%	31.18%	-	-	-	-
Total number of doses per patient per year														
Upadacitinib	349.82	311.34	277.09	246.61	219.48	195.34	173.85	154.73	137.71	122.56	-	-	-	-
Ixekizumab	13.98	11.12	9.90	8.81	7.84	6.98	6.21	5.53	4.92	4.38	-	-	-	-
Secukinumab	15.49	10.23	9.10	8.10	7.21	6.42	5.71	5.08	4.52	4.03	-	-	-	-
Total undiscounted costs														
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	£16,484	£12,789	£11,382	£10,130	£9,016	£8,024	£7,141	£6,356	£5,657	£5,034	£29,273	£59,801	£86,979	£92,014
Secukinumab	£10,199	£6,513	£5,797	£5,159	£4,592	£4,087	£3,637	£3,237	£2,881	£2,564	£16,712	£32,260	£46,101	£48,665
Incremental undiscounted costs (A)														
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Other costs and analyses

B9. Symptoms of extra-articular manifestations in AS may impact on treatment decisions including selection of biologic drugs and whether to continue treatment. Please comment on the appropriateness of excluding uveitis outcomes and their associated costs from the cost-comparison model.

Clinicians determine the optimal treatment for their AS patients with extra-articular manifestations. However, once this optimal treatment has been initiated, cost of treating uveitis, and associated outcomes, are comparable. Hence, this has minimal impact on cost-effectiveness outcomes and there is no requirement to model comparable costs and outcomes in the economic model. Further, given the poor reporting of data to inform the proportion of patients experiencing the costs and outcomes (described in response to Question A13), this may lead to more uncertainty than is addressed.

Section C: Textual clarification and additional points

Textual clarifications

C1. Table 4 in the main company submission: should the heading of the 3rd column read 'CEA or CCA'?

Yes, the heading of the third column of Table 4 should read "CEA or CCA."

C2. Section B.3.6.2.6, page 55 of the main submission: please check the details given for the p-value quoted in the following text "…to handle missing data due to COVID-19, showed a statistically higher response rate (p > 0.0001)…".

There is an error in the greater than sign for the p-value. This sentence should read: "The primary analysis using non-responder imputation in conjunction with multiple imputation (NRI-MI) to handle missing data due to COVID-19, showed a statistically higher response rate (p < 0.0001) in the upadacitinib group (44.5%) compared to the placebo group (18.2%)."

C3. Section B.4.2.1, page 94: please check the following sentence for any missing words or explain its meaning "Whilst discontinuation rates are

decidedly comparable across treatments and the base case adopts an approach considered appropriate in the most recent AS technology appraisals."

This sentence should read:
"Whilst discontinuation rates are comparable across treatments, the base case adopts the approach considered appropriate in the most recent AS technology appraisals, where discontinuation probabilities were applied at 3-monthly intervals to each treatment."

Cost-comparison

C4. Previous appraisals in ankylosing spondylitis have used the unit cost of a rheumatology specialist visits (£149.14, currency code WF01A: Consultant-led non-admitted face-to-face attendance, follow-up) from the National Schedule of NHS Costs 2019-2020 main schedule[51] to estimate the cost of specialist visits. In contrast, the company has chosen to apply the corresponding unit cost across all HRGs (£125.44). Please update this model parameter so that is consistent with previous appraisals (i.e., use the unit cost of £149.14)

As suggested, this has been updated this cost in line with the unit cost of a rheumatology specialist visits (£149.14, currency code WF01A: Consultant-led non-admitted face-to-face attendance, follow-up). Importantly, the cost is taken from National schedule of NHS costs v2 (NHS Reference Costs 2019/20),[52] which includes amendments to the original National schedule of NHS costs.

As other amendments have been made to the base case cost-comparison analysis (in response to questions B6, B7, C4 and C6), please see the response to question B6 for updated results corresponding to all of these changes.

C5. The ERG could not validate the unit cost estimate applied by the company to full blood count and erythrocyte sedimentation rate for (see Table 35, main company submission) against the National Schedule of NHS Costs 2019-2020 main schedule.[51] The unit cost for the currency code cited (DAPS05 - Total Other Currencies) is £2.53. whereas the company uses £2.56. Similarly, the unit cost for the currency code cited for antinuclear antibodies and DNA

double strand test (DAP06 - Other Currencies) does not match the value in the source (£7.40 instead of £7.35). Please correct the unit costs as appropriate.

AbbVie believes these costs to be correct and thus no amendment has been made. The cost is taken from National Cost Collection data Version 2 (NHS Reference Costs 2019/20).[52] which includes amendments to the original National Cost Collection data. AbbVie believes the clarification question refers to the original version of the National Cost Collection data.

C6. Please justify the currency code chosen to inform the unit costs for a chest X-Ray, and consider applying instead the currency code DAPF- Direct access plain film (as per TA718), which corresponds to a unit cost of £32.72.

As suggested, AbbVie have updated this cost in line with the unit cost of DAPF - Direct access plain film (as per TA718), which corresponds to a unit cost of £32.65. Importantly, the cost is taken from National schedule of NHS costs v2 (NHS Reference Costs 2019/20), which includes amendments to the original National schedule of NHS costs.[52]

As other amendments have been made to the base case cost-comparison analysis (in response to questions B6, B7, C4 and C6), please see the response to question B6 for updated results corresponding to all of these changes.

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Appendix A

Table 16. Exclusion reasons for records retrieved from LILACS database (n=34)

#	Citation	Reason for exclusion
1.	Aikawa NE, Rosa DTA, Del Negro GMB, et al. Systemic and localized infection by Candida species in patients with rheumatic diseases receiving anti-TNF therapy. *Rev. bras. reumatol.* 2016;56(6):478-482.	Ineligible study design (stand-alone safety study) Identified and excluded in original SLR
2.	Antonio JR, Sanmiguel J, Cagnon GV, Augusto MSF, Godoy MFd, Pozetti EMO. Infliximab in patients with psoriasis and other inflammatory diseases: evaluation of adverse events in the treatment of 168 patients. *An. bras. dermatol.* 2016;91(3):306-310.	Ineligible study design (stand-alone safety study) Identified and excluded in original SLR
3.	Brasil. Ministério da Saúde. Comissão Nacional de Incorporação de Tecnologias no SUS. Golimumabe para o tratamento da espondilite ancilosante. 2016.	Ineligible study design (HTA decision from agency not outlined in protocol)
4.	Brasil. Ministério da Saúde. Secretaria de Ciência TeIE. Golimumabe para espondilite anquilosante. 2013.	Ineligible study design (HTA decision from agency not outlined in protocol)
5.	Brasil. Ministério da Saúde. Secretaria de Ciência TeIE. Certolizumabe pegol para o tratamento de espondiloartrite axial. 2017.	Ineligible study design (HTA decision from agency not outlined in protocol)
6.	Brasil. Ministério da Saúde. Secretaria de Ciência TeIE. Secuquinumabe para o tratamento da espondilite anquilosante. 2018.	Ineligible study design (HTA decision from agency not outlined in protocol)
7.	Callado MRM, Lima JRC, Nobre CA, Vieira WP. Baixa prevalência de PPD reativo prévia ao uso de infliximabe: estudo comparativo em população amostral do Hospital Geral de Fortaleza. *Rev. bras. reumatol.* 2011;51(1):46-52.	Ineligible study design (stand-alone safety study)
8.	Campos Neto OH, Acurcio FdA, Machado MAdÁ, et al. Médicos, advogados e indústria farmacêutica na judicialização da saúde em Minas Gerais, Brasil. *Rev. saúde pública.* 2012;46(5):784-790.	Wrong outcomes
9.	Cavalieri M, Schneeberger EE, Dal Pra F, et al. Patrones de tratamiento con agentes biológicos, eficacia y sobrevida a largo plazo en pacientes con espondiloartritis axial: Impacto de los factores sociodemográficos en Latinoamérica. *Rev. argent. reumatol.* 2018;29(4):22-28.	Wrong population (axSpA but AS not specified)
10.	Chile. Ministerio de S. Informe de evaluación científica basada en la evidencia disponible: espondilitis anquilosante. 2017.	Ineligible study design (HTA decision from agency not outlined in protocol)
11.	Chiuchetta FA. Criptosporidiose em paciente com espondilite anquilosante usando adalimumabe. *Rev. bras. reumatol.* 2010;50(3):328-332.	Ineligible study design (<10 patients, case report, stand-alone safety study)
12.	Dabés CGeS, Almeida AM, Acurcio FdA. Não adesão à terapia biológica em pacientes com doenças reumáticas no Sistema Único de Saúde em Minas Gerais, Brasil. *Cad. saúde pública.* 2015;31(12):2599-2609.	Wrong outcomes
13.	Del Pintor Bidoia F, Vinicius Mendes Roncada E, Vasconcelos Schaefer L, Aparecida Milanez Morgado de	Ineligible study design (<10 patients and case report)

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	Abreu M, Shimizu GKM, Gasparini KT. Psoríase pustulosa palmoplantar como efeito paradoxal do uso de adalimumabe: relato de caso. *Diagn. tratamento.* 2018;23(2):45-49.	
14.	Díaz Verdúzco MdJ. Dos casos de reactivación de tuberculosis pulmonar por infliximab: Problemas y propuestas de solución. *Rev. Inst. Nac. Enfermedades Respir.* 2005;18(1):27-37.	Ineligible study design (<10 patients and case report)
15.	Gomes KWP, Benevides AN, Vieira FJF, Burlamaqui MPdM, Vieira MdAeP, Fontenelle LMAR. Leishmaniose tegumentar em paciente com espondilite anquilosante utilizando adalimumabe. *Rev. bras. reumatol.* 2012;52(3):450-452.	Ineligible study design (<10 patients and case report)
16.	Hwang J, Kim H-M, Jeong H, et al. Higher body mass index and anti-drug antibodies predict the discontinuation of anti-TNF agents in Korean patients with axial spondyloarthritis. *Rev. bras. reumatol.* 2017;57(4):311-319.	Wrong population (axSpA but AS not specified) Identified and excluded in original SLR
17.	Machado J, Moncada JC, Pineda R. Perfil de utilización de los anti-factor de necrosis tumoral en pacientes de Colombia. *Biomédica (Bogotá).* 2011;31(2):250-257.	Ineligible study design (observational study)
18.	Machado NP, Reis Neto ETd, Soares MRMP, et al. The skin tissue is adversely affected by TNF-alpha blockers in patients with chronic inflammatory arthritis: a 5-year prospective analysis. *Clinics.* 2013;68(9):1189-1196.	Ineligible study design (stand-alone safety study) Identified and excluded in original SLR
19.	Márquez JR, Gomollón F. El papel de los biosimilares en la enfermedad inflamatoria intestinal: una realidad en nuestro país. *Rev. colomb. gastroenterol.* 2017;32(4):311-325.	Ineligible study design (review)
20.	Montero M, García Poma A, Chung Nakandakari CP, Chávez Corrales JE, Segami Salazar MI. Infliximab en pacientes con espondilitis anquilosante activa: experiencia en el Hospital Nacional Edgardo Rebagliati Martins. *An. Fac. Med. (Perú).* 2007;68(2):175-180.	Ineligible study design (<10 patients)
21.	Moraes JCBd. Efeito da inflamação no peptídeo natriurético atrial (NT-proBNP) em pacientes com espondilite anquilosante ativa durante terapia anti-TNF. 2013:[77]-[77].	Wrong outcome
22.	Moraes JCBd, Aikawa NE, Ribeiro ACdM, et al. Complicações imediatas de 3.555 aplicações de agentes anti-TNF&#945. *Rev. bras. reumatol.* 2010;50(2):165-175.	Ineligible study design (observational study and stand-alone safety study)
23.	Nascimento Júnior RRd, Jesus DXd, Rehen NN, Pedra DdSAM. Análise clínica e econômica de "mundo real" da substituição do medicamento Remicade® (infliximabe referência) por Remsima™ (infliximabe biossimilar) em pacientes com artrite reumatoide, espondilite anquilosante e artrite psoriática. *J. bras. econ. saúde (Impr.).* 2019;11(2):119-127.	Ineligible study design (observational study)
24.	Oliveira Junior HAd, Almeida AM, Acurcio FA, et al. Profile of patients with rheumatic diseases undergoing treatment with anti-TNF agents in the Brazilian Public Health System (SUS), Belo Horizonte - MG. *Braz. j. pharm. sci.* 2015;51(3):709-719.	Ineligible study design (prospective observational study) Identified and excluded in original SLR
25.	Perú. EsSalud. Instituto de Evaluación de Tecnologías en Salud e I. Eficácia y seguridad de adalimumab en el tratamiento de espondilitis anquilosante en pacientes con falla a tratamiento com dos anti-TNFS. 2016.	Ineligible study design (review)

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26.	Rozenfeld Levites M, Subtil de Paula P, Bogea Müller de Almeida L, Polesel Federicil V. Acurácia do teste imunoquímico fecal (pesquisa de sangue oculto) na triagem do câncer colorretal. *Diagn. tratamento.* 2018;23(2):[50]-[51].	Wrong population
27.	Santos P, Londoño J, Velez P, Avila M, Valle R. Eficacia y seguridad del infliximab en una cohorte de pacientes colombianos con Espondiloartropatias. *Rev. colomb. reumatol.* 2003;10(4):293-301.	Wrong population (other conditions included)
28.	Silva BSPd, Endo AC, Medeiros ACd, et al. Frequency of antibodies against the etiologic agents of acquired imunodeficiency syndrome, syphilis, hepatitis B and C, and Chagas' disease in patients with rheumatic diseases treated with anti-tumor necrosis factor. *Rev. bras. reumatol.* 2009;49(5):590-598.	Wrong outcomes Identified and excluded in original SLR
29.	Silva ILAFe. Imunogenicidade e segurança da vacina contra influenza A H1N1/2009 em pacientes com doenças reumáticas em uso de terapia anti-TNF alfa. 2014:[57]-[57].	Wrong intervention
30.	Silva TS, Guimarães CLM, Xavier IP, Rego VRPdA. Lobular capillary hemangioma in a patient with ankylosing spondylitis using adalimumab: an exuberant presentation. *An. bras. dermatol.* 2019;94(6):751-753.	Ineligible study design (<10 patients and case report) Identified and excluded in original SLR
31.	Strusberg I, Bertoli AM, de Pizzolato RC, Fierro G, Strusberg AM. Uso de infliximab en pacientes de un centro reumatologico. *Medicina (B.Aires).* 2005;65(1):24-30.	Ineligible study design (observational study)
32.	Ugarte-Gil MF, Acevedo-Vásquez EM, Alarcón GS. Terapia biológica en enfermedades reumatológicas. *Rev. méd. hered.* 2013;24(2):141-155.	Ineligible study design (review)
33.	Vaz JLP, Andrade CAF, Pereira AC, Martins MdFM, Levy RA. Revisão sistemática da indução de autoanticorpos e lúpus eritematoso pelo infliximabe. *Rev. bras. reumatol.* 2013;53(4):358-364.	Ineligible study design (review)
34.	Zengin O, Onder ME, Alkan S, et al. Three cases of anti-TNF induced myositis and literature review. *Rev. bras. reumatol.* 2017;57(6):590-595.	Ineligible study design (<10 patients and case report) Identified and excluded in original SLR

Appendix B

The search strategy and results from the updated clinical SLR are presented in Table 17 to Table 23.

The search strategy and results from the updated economic SLR are presented in Table 24 to Table 28.

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Table 17. Ovid Embase: 1974 to 2021 October 27 (Searched: 28.10.21)

1	spondylarthritis/	9664
2	((Ankyl* or Axial*) adj2 (spondyl* or spine or spinal or verteb*)).ti,ab,kw,ot.	29676
3	(axial SpA or axSpA or nr-axSpA or SpA).ti,ab,kw,ot.	21012
4	(Bechterew* or bekhterev* or marie stru?mpell* or marie-struempell* or "Strumpell–Marie disease" or (Marie* adj disease) or (Pierre Marie* adj disease)).ti,ab,kw,ot.	869
5	1 or 2 or 3 or 4	48573
6	upadacitinib/	923
7	(Upadacitinib* or Rinvoq* or ABT 494 or ABT494 or ABT-494 or 4RA0KN46E0 or 1310726-60-3).af.	958
8	adalimumab/	38156
9	(Adalimumab* or adalimumab-adaz or adalimumab-adbm or adalimumab-afzb or adalimumab-atto or adalimumab-bwwd or Hadlima* or Humira* or Imraldi* or Amjevita* or Cyltezo* or Trudexa* or abp-501 or ABP 501 or bcd-057 or bi-695501 or bi695501 or chs-1420 or d2e7 or gp-2017 or gp2017 or lu-200134 or lu200134 or m-923 or m923 or msb-11022 or msb11022 or ons-3010 or sb-5 or sb5 or fys6t7f842 or FYS6T7F842 or 331731-18-1).af.	39453
10	certolizumab pegol/	7652
11	(Certolizumab* or Cimzia* or CDP 870 or CDP-870 or CDP870 or PHA-738144 or pha 738144 or pha738144 or UMD07X179E or 428863-50-7).af.	8370
12	etanercept/	33963
13	(Etanercept* or etanercept-szzs or etanercept-ykro or Recombinant human TNF or rhu TNFR:Fc or rhu-TNFR:Fc or TNFR-Immunoadhesin or TNFR Fc or "tnr 001" or tnr001 or Brenzys* or benepali* or Enbrel* or embrel* or Erelzi* or Davictrel* or Tunex* or altebrel* or CHS-0214 or DWP-422 or ENIA-11 or GP-2015 or GP2015 or GP2015C or HD-203 or HD203 or LBEC-0101 or LBEC0101 or SB-4 or SB4 or enia 11 or enia11 or OP401G7OJC or 185243-69-0 or 200013-86-1 or 2055118-96-0).af.	36009
14	golimumab/	8181
15	(Golimumab* or Simponi* or CNTO 148 or CNTO-148 or 91X1KLU43E or 476181-74-5).af.	8383
16	infliximab/	55254
17	(infliximab* or Infliximab-abda or Infliximab-axxq or Infliximab-dyyb or Infliximab-qbtx or Avsola* or Flixabi* or Inflectra* or Avsola* or avakine* or INFLIX* or ixifi* or Remicade* or Remsima* or Renflexis* or revellex* or zessly* or ABP 710 or ABP-710 or BOW-015 or BOW015 or CT-P-13 or CT-P13 or GP 1111 or GP-1111 or PF-06438179 or "PF 06438179" or pf 6438179 or pf06438179 or pf6438179 or TA-650 or SB2 or B72HH48FLU or 170277-31-3).af.	57204
18	ixekizumab/	2445
19	(Ixekizumab* or taltz* or LY 2439821 or LY-2439821 or LY2439821 or BTY153760O or 1143503-69-8).af.	2546
20	tofacitinib/	6108
21	(Tofacitinib* or Tasocitinib* or Tofacitinibum* or Xeljanz* or CP 690550 or CP- 690 550 or CP-690 or CP-690-550 or CP-690,550 or CP-690550 or CP690,550 or CP690550 or cp690550 10 or cp690550-10 or 87LA6FU830 or 477600-75-2 or 540737-29-9).af.	6605
22	secukinumab/	5023
23	(secukinumab* or Cosentyx* or AIN-457 or AIN457 or AIN457A or DLG4EML025 or 1229022-83-6 or 875356-43-7 or 875356-44-8).af.	5225
24	filgotinib/	666
25	(filgotinib* or g 146034 or g 146034-101 or g146034 or g146034-101 or "glpg 0634" or glpg0634 or GS-6034 or 3XVL385Q0M or 1206161-97-8 or 1540859-07-1).af.	720
26	bimekizumab/	202
27	(Bimekizumab* or UCB4940 or 09495UIM6V or 1418205-77-2).af.	212
28	(Hulio* or Imraldi* or Hefiya* or Amgevita* or Idacio* or Hyrimoz* or Halimatoz* or Amsparity* or Erelzi* or Benepali* or Zessly* or Flixabi*).af.	349

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29	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	94654
30	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	0
31	Randomized Controlled Trial/	681432
32	exp Randomized Controlled Trials as Topic/	213579
33	"Randomized Controlled Trial (topic)"/	213492
34	Controlled Clinical Trial/	464256
35	exp Controlled Clinical Trials as Topic/	221885
36	"Controlled Clinical Trial (topic)"/	11976
37	Randomization/	92107
38	Random Allocation/	88284
39	Double-Blind Method/	164615
40	Double Blind Procedure/	189030
41	Double-Blind Studies/	147964
42	Single-Blind Method/	42158
43	Single Blind Procedure/	44170
44	Single-Blind Studies/	44170
45	Placebos/	316872
46	Placebo/	372773
47	Control Groups/	109743
48	Control Group/	109743
49	(random* or sham or placebo*).ti,ab,hw,kw.	2254255
50	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	328779
51	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	1655
52	(control* adj3 (study or studies or trial* or group*)).ti,ab,kw.	1508210
53	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom* or "single arm").ti,ab,hw,kw.	81106
54	allocated.ti,ab,hw.	95036
55	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kw.	73192
56	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kw.	14541
57	(pragmatic study or pragmatic studies).ti,ab,hw,kw.	728
58	((pragmatic or practical) adj3 trial*).ti,ab,hw,kw.	6548
59	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kw.	15416
60	(phase adj3 (II or III or "2" or "3") adj3 (study or studies or trial*)).ti,hw,kw.	214358
61	(trial or trail).ti.	349326
62	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61	3469255
63	(safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab,kw.	2604605
64	"systematic review"/	318619
65	(systematic$ adj3 review$).ti,ab,ot,hw,kw.	425699
66	meta analysis/	228494
67	meta anal$.ti,ab,ot,hw,kw.	358079
68	64 or 65 or 66 or 67	588228
69	62 or 63 or 68	5702973
70	5 and 29 and 69	3953
71	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp.	7104564
72	70 not 71	3826
73	(conference abstract or conference review).pt.	4243990
74	72 not 73	1944
75	limit 74 to dc=20210325-20211028	150

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Table 18. Ovid Embase: 1974 to 2021 October 27 (Searched: 28.10.21)

1	spondylarthritis/	9664
2	((Ankyl* or Axial*) adj2 (spondyl* or spine or spinal or verteb*)).ti,ab,kw,ot.	29676
3	(axial SpA or axSpA or nr-axSpA or SpA).ti,ab,kw,ot.	21012
4	(Bechterew* or bekhterev* or marie stru?mpell* or marie-struempell* or "Strumpell–Marie disease" or (Marie* adj disease) or (Pierre Marie* adj disease)).ti,ab,kw,ot.	869
5	1 or 2 or 3 or 4	48573
6	upadacitinib/	923
7	(Upadacitinib* or Rinvoq* or ABT 494 or ABT494 or ABT-494 or 4RA0KN46E0 or 1310726-60-3).af.	958
8	adalimumab/	38156
9	(Adalimumab* or adalimumab-adaz or adalimumab-adbm or adalimumab-afzb or adalimumab-atto or adalimumab-bwwd or Hadlima* or Humira* or Imraldi* or Amjevita* or Cyltezo* or Trudexa* or abp-501 or ABP 501 or bcd-057 or bi-695501 or bi695501 or chs-1420 or d2e7 or gp-2017 or gp2017 or lu-200134 or lu200134 or m-923 or m923 or msb-11022 or msb11022 or ons-3010 or sb-5 or sb5 or fys6t7f842 or FYS6T7F842 or 331731-18-1).af.	39453
10	certolizumab pegol/	7652
11	(Certolizumab* or Cimzia* or CDP 870 or CDP-870 or CDP870 or PHA-738144 or pha 738144 or pha738144 or UMD07X179E or 428863-50-7).af.	8370
12	etanercept/	33963
13	(Etanercept* or etanercept-szzs or etanercept-ykro or Recombinant human TNF or rhu TNFR:Fc or rhu-TNFR:Fc or TNFR-Immunoadhesin or TNFR Fc or "tnr 001" or tnr001 or Brenzys* or benepali* or Enbrel* or embrel* or Erelzi* or Davictrel* or Tunex* or altebrel* or CHS-0214 or DWP-422 or ENIA-11 or GP-2015 or GP2015 or GP2015C or HD-203 or HD203 or LBEC-0101 or LBEC0101 or SB-4 or SB4 or enia 11 or enia11 or OP401G7OJC or 185243-69-0 or 200013-86-1 or 2055118-96-0).af.	36009
14	golimumab/	8181
15	(Golimumab* or Simponi* or CNTO 148 or CNTO-148 or 91X1KLU43E or 476181-74-5).af.	8383
16	infliximab/	55254
17	(infliximab* or Infliximab-abda or Infliximab-axxq or Infliximab-dyyb or Infliximab-qbtx or Avsola* or Flixabi* or Inflectra* or Avsola* or avakine* or INFLIX* or ixifi* or Remicade* or Remsima* or Renflexis* or revellex* or zessly* or ABP 710 or ABP-710 or BOW-015 or BOW015 or CT-P-13 or CT-P13 or GP 1111 or GP-1111 or PF-06438179 or "PF 06438179" or pf 6438179 or pf06438179 or pf6438179 or TA-650 or SB2 or B72HH48FLU or 170277-31-3).af.	57204
18	ixekizumab/	2445
19	(Ixekizumab* or taltz* or LY 2439821 or LY-2439821 or LY2439821 or BTY153760O or 1143503-69-8).af.	2546
20	tofacitinib/	6108
21	(Tofacitinib* or Tasocitinib* or Tofacitinibum* or Xeljanz* or CP 690550 or CP- 690 550 or CP-690 or CP-690-550 or CP-690,550 or CP-690550 or CP690,550 or CP690550 or cp690550 10 or cp690550-10 or 87LA6FU830 or 477600-75-2 or 540737-29-9).af.	6605
22	secukinumab/	5023
23	(secukinumab* or Cosentyx* or AIN-457 or AIN457 or AIN457A or DLG4EML025 or 1229022-83-6 or 875356-43-7 or 875356-44-8).af.	5225
24	filgotinib/	666
25	(filgotinib* or g 146034 or g 146034-101 or g146034 or g146034-101 or "glpg 0634" or glpg0634 or GS-6034 or 3XVL385Q0M or 1206161-97-8 or 1540859-07-1).af.	720
26	bimekizumab/	202
27	(Bimekizumab* or UCB4940 or 09495UIM6V or 1418205-77-2).af.	212

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28	(Hulio* or Imraldi* or Hefiya* or Amgevita* or Idacio* or Hyrimoz* or Halimatoz* or Amsparity* or Erelzi* or Benepali* or Zessly* or Flixabi*).af.	349
29	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	94654
30	(conference abstract or conference review).pt.	4243990
31	5 and 29 and 30	3314
32	(2020* or 2021*).yr.	3278405
33	31 and 32	503
34	limit 33 to dc=20210325-20211028	202

Table 19. Ovid MEDLINE(R) ALL: 1946 to October 27, 2021 (Searched: 28.10.21)

1	Spondylitis, Ankylosing/	15442
2	((Ankyl* or Axial*) adj2 (spondyl* or spine or spinal or verteb*)).ti,ab,kw,ot,kf.	18628
3	(axial SpA or axSpA or nr-axSpA or SpA).ti,ab,kw,ot,kf.	12920
4	(Bechterew* or bekhterev* or marie stru?mpell* or marie-struempell* or "Strumpell–Marie disease" or (Marie* adj disease) or (Pierre Marie* adj disease)).ti,ab,kw,ot,kf.	896
5	1 or 2 or 3 or 4	33345
6	(Upadacitinib* or Rinvoq* or ABT 494 or ABT494 or ABT-494 or 4RA0KN46E0 or 1310726-60-3).af.	240
7	Adalimumab/	6071
8	(Adalimumab* or adalimumab-adaz or adalimumab-adbm or adalimumab-afzb or adalimumab-atto or adalimumab-bwwd or Hadlima* or Humira* or Imraldi* or Amjevita* or Cyltezo* or Trudexa* or abp-501 or ABP 501 or bcd-057 or bi-695501 or bi695501 or chs-1420 or d2e7 or gp-2017 or gp2017 or lu-200134 or lu200134 or m-923 or m923 or msb-11022 or msb11022 or ons-3010 or sb-5 or sb5 or fys6t7f842 or FYS6T7F842 or 331731-18-1).af.	10051
9	Certolizumab Pegol/	677
10	(Certolizumab* or Cimzia* or CDP 870 or CDP-870 or CDP870 or PHA-738144 or pha 738144 or pha738144 or UMD07X179E or 428863-50-7).af.	1458
11	Etanercept/	6160
12	(Etanercept* or etanercept-szzs or etanercept-ykro or Recombinant human TNF or "rhu TNFR:Fc" or "rhu-TNFR:Fc" or TNFR-Immunoadhesin or TNFR Fc or "tnr 001" or tnr001 or Brenzys* or benepali* or Enbrel* or embrel* or Erelzi* or Davictrel* or Tunex* or altebrel* or CHS-0214 or DWP-422 or ENIA-11 or GP-2015 or GP2015 or GP2015C or HD-203 or HD203 or LBEC-0101 or LBEC0101 or SB-4 or SB4 or enia 11 or enia11 or OP401G7OJC or 185243-69-0 or 200013-86-1 or 2055118-96-0).af.	9926
13	(Golimumab* or Simponi* or CNTO 148 or CNTO-148 or 91X1KLU43E or 476181-74-5).af.	1426
14	Infliximab/	11091
15	(infliximab* or Infliximab-abda or Infliximab-axxq or Infliximab-dyyb or Infliximab-qbtx or Avsola* or Flixabi* or Inflectra* or Avsola* or avakine* or INFLIX* or ixifi* or Remicade* or Remsima* or Renflexis* or revellex* or zessly* or ABP 710 or ABP-710 or BOW-015 or BOW015 or CT-P-13 or CT-P13 or GP 1111 or GP-1111 or PF-06438179 or "PF 06438179" or pf 6438179 or pf06438179 or pf6438179 or TA-650 or SB2 or B72HH48FLU or 170277-31-3).af.	16661
16	(Ixekizumab* or taltz* or LY 2439821 or LY-2439821 or LY2439821 or BTY153760O or 1143503-69-8).af.	759
17	(Tofacitinib* or Tasocitinib* or Tofacitinibum* or Xeljanz* or CP 690550 or CP- 690 550 or CP-690 or CP-690-550 or CP-690,550 or CP-690550 or CP690,550 or CP690550 or cp690550 10 or cp690550-10 or 87LA6FU830 or 477600-75-2 or 540737-29-9).af.	2037
18	(secukinumab* or Cosentyx* or AIN-457 or AIN457 or AIN457A or DLG4EML025 or 1229022-83-6 or 875356-43-7 or 875356-44-8).af.	1500
19	(filgotinib* or g 146034 or g 146034-101 or g146034 or g146034-101 or "glpg 0634" or glpg0634 or GS-6034 or 3XVL385Q0M or 1206161-97-8 or 1540859-07-1).af.	170

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20	(Bimekizumab* or UCB4940 or 09495UIM6V or 1418205-77-2).af.	65
21	(Hulio or Imraldi or Hefiya or Amgevita or Idacio or Hyrimoz or Halimatoz or Amsparity or Erelzi or Benepali or Zessly or Flixabi).af.	79
22	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	31318
23	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	642129
24	Randomized Controlled Trial/	548303
25	exp Randomized Controlled Trials as Topic/	153273
26	"Randomized Controlled Trial (topic)"/	0
27	Controlled Clinical Trial/	94492
28	exp Controlled Clinical Trials as Topic/	158886
29	"Controlled Clinical Trial (topic)"/	0
30	Randomization/	106097
31	Random Allocation/	106097
32	Double-Blind Method/	167924
33	Double Blind Procedure/	0
34	Double-Blind Studies/	167924
35	Single-Blind Method/	31072
36	Single Blind Procedure/	0
37	Single-Blind Studies/	31072
38	Placebos/	35730
39	Placebo/	0
40	Control Groups/	1780
41	Control Group/	1780
42	(random* or sham or placebo*).ti,ab,hw,kf,kw.	1638470
43	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	251492
44	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	1270
45	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	1089335
46	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom* or "single arm").ti,ab,hw,kw.	57813
47	allocated.ti,ab,hw.	73834
48	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	39108
49	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	9985
50	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	492
51	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	6394
52	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	9631
53	(phase adj3 (II or III or "2" or "3") adj3 (study or studies or trial*)).ti,hw,ab.	117432
54	(trial or trail).ti.	256154
55	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54	2452926
56	adverse effects/ or ae.fs.	1847752
57	(safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.	1773757
58	56 or 57	3202331
59	systematic review/ or (systematic$ adj3 review$).ti,ab,ot,hw,kw.	261290
60	meta analysis/ or meta anal$.ti,ab,kw.	240054
61	59 or 60	377426
62	55 or 58 or 61	5240784
63	5 and 22 and 62	1504
64	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp.	7563082
65	animals/ not (animals/ and humans/)	4872240

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66	64 or 65	7563082
67	63 not 66	1422
68	limit 67 to dt=20210325-20211028	**52**

Table 20. PubMed (https://pubmed.ncbi.nlm.nih.gov/)
Searched: 28.10.21

((((((Upadacitinib* OR Adalimumab* OR Certolizumab* OR Etanercept* OR Davictrel* OR Golimumab* OR infliximab*OR INFLIX* OR Ixekizumab* OR Tofacitinib* OR secukinumab* OR filgotinib* OR Hulio* or Imraldi* or Hefiya* or Amgevita* or Idacio* or Hyrimoz* or Halimatoz* or Amsparity* or Erelzi* or Benepali* or Zessly* or Flixab* or Bimekizumab*))))) AND ankylosing spondylitis) AND ((((((((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]))))))))

Date limit: 25.3.21 – 28.10.21
49 results

Table 21. CDSR: Issue 12, October 2021 and CENTRAL: Issue 12, October 2021 (Searched: 28.10.21)

#1	MeSH descriptor: [Spondylitis, Ankylosing] this term only	718
#2	((Ankyl* or Axial*) NEAR/2 (spondyl* or spine or spinal or verteb*)):ti,ab	2365
#3	(axial SpA or axSpA or nr-axSpA or SpA):ti,ab	1519
#4	(Bechterew* or bekhterev* or marie stru?mpell* or marie-struempell* or "Strumpell–Marie disease" or (Marie* NEAR/1 disease) or (Pierre Marie* NEAR/1disease)):ti,ab	30
#5	#1 or #2 or #3 or #4	3458
#6	(Upadacitinib* or Rinvoq* or ABT 494 or ABT494 or ABT-494 or 4RA0KN46E0 or "1310726-60-3"):ti,ab	411
#7	(Adalimumab* or adalimumab-adaz or adalimumab-adbm or adalimumab-afzb or adalimumab-atto or adalimumab-bwwd or Hadlima* or Humira* or Imraldi* or Amjevita* or Cyltezo* or Trudexa* or abp-501 or ABP 501 or bcd-057 or bi-695501 or bi695501 or chs-1420 or d2e7 or gp-2017 or gp2017 or lu-200134 or lu200134 or m-923 or m923 or msb-11022 or msb11022 or ons-3010 or sb-5 or sb5 or fys6t7f842 or FYS6T7F842 or "331731-18-1"):ti,ab	3344
#8	(Certolizumab* or Cimzia* or CDP 870 or CDP-870 or CDP870 or PHA-738144 or pha 738144 or pha738144 or UMD07X179E or "428863-50-7"):ti,ab	695
#9	(Etanercept* or Recombinant human TNF or rhu TNFRFc or "TNFR Immunoadhesin" or TNFR Fc or "tnr 001" or tnr001 or Brenzys* or benepali* or Enbrel* or embrel* or Erelzi* or Davictrel* or Tunex* or altebrel* or CHS-0214 or DWP-422 or ENIA-11 or GP-2015 or GP2015 or GP2015C or HD-203 or HD203 or LBEC-0101 or LBEC0101 or SB-4 or SB4 or enia 11 or enia11 or OP401G7OJC or "185243-69-0" or "200013-86-1" or "2055118-96-0"):ti,ab	2395
#10	(Golimumab* or Simponi* or CNTO 148 or CNTO-148 or 91X1KLU43E or "476181-74-5"):ti,ab	733
#11	(infliximab* or Avsola* or Flixabi* or Inflectra* or Avsola* or avakine* or INFLIX* or ixifi* or Remicade* or Remsima* or Renflexis* or revellex* or zessly* or ABP 710 or ABP-710 or BOW-015 or BOW015 or CT-P-13 or CT-P13 or GP 1111 or GP-1111 or "PF-06438179" or "PF 06438179" or pf 6438179 or pf06438179 or pf6438179 or TA-650 or SB2 or B72HH48FLU or "170277-31-3")	3221
#12	(Ixekizumab* or taltz* or LY 2439821 or LY-2439821 or LY2439821 or BTY153760O or "1143503-69-8"):ti,ab	546
#13	(Tofacitinib* or Tasocitinib* or Tofacitinibum* or Xeljanz* or CP 690550 or "CP-690 550" or CP-690 or "CP-690-550" or "CP-690,550" or "CP-690550" or "CP690,550" or CP690550 or cp690550 10 or "cp690550-10" or 87LA6FU830 or "477600-75-2" or "540737-29-9"):ti,ab	902

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#14	(secukinumab* or Cosentyx* or AIN-457 or AIN457 or AIN457A or DLG4EML025 or "1229022-83-6" or "875356-43-7" or "875356-44-8"):ti,ab	1004
#15	(filgotinib* or g 146034 or "g 146034-101" or g146034 or "g146034-101" or "glpg 0634" or glpg0634 or GS-6034 or 3XVL385Q0M or "1206161-97-8" or "1540859-07-1"):ti,ab	247
#16	(Bimekizumab* OR UCB4940 or 09495UIM6V or "1418205-77-2"):ti,ab	107
#17	(Hulio or Imraldi or Hefiya or Amgevita or Idacio or Hyrimoz or Halimatoz or Amsparity or Erelzi or Benepali or Zessly or Flixabi):ti,ab	30
#18	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17	11415
#19	#5 and #18 with Cochrane Library publication date Between Mar 2021 and Oct 2021	102

CDSR = 0
CENTRAL =102

Table 22. International HTA Database (https://database.inahta.org/) (Searched: 28.10.21)

1. Axial Spondyloarthritis n=1;
2. Ankylosing spondylitis n=0
Nothing new added since 25.3.21

Table 23. LILACS (https://lilacs.bvsalud.org/en/) (Searched: 28.10.21)

tw:((tw:((((axial spondyloarthritis) OR (axspa) OR (ankylosing spondylitis))))) AND (tw:(((upadacitinib* OR adalimumab* OR certolizumab* OR etanercept* OR davictrel* OR golimumab* OR infliximab*or inflix* OR ixekizumab* OR tofacitinib* OR secukinumab* OR filgotinib* OR hulio* OR imraldi* OR hefiya* OR amgevita* OR idacio* OR hyrimoz* OR halimatoz* OR amsparity* OR erelzi* OR benepali* OR zessly* OR flixab* OR bimekizumab*))))) AND (db:("LILACS") AND la:("en"))
2021-2021, English language
0 results

Table 24. Embase: 1974 to 2021 October 27 (Searched: 28.10.21)

1	spondylarthritis/	9664
2	((Ankyl* or Axial*) adj2 (spondyl* or spine or spinal or verteb*)).ti,ab,kw,ot.	29676
3	(axial SpA or axSpA or nr-axSpA or SpA).ti,ab,kw,ot.	21012
4	(Bechterew* or bekhterev* or marie stru?mpell* or marie-struempell* or "Strumpell–Marie disease" or (Marie* adj disease) or (Pierre Marie* adj disease)).ti,ab,kw,ot.	869
5	1 or 2 or 3 or 4	48573
6	upadacitinib/	923
7	(Upadacitinib* or Rinvoq* or ABT 494 or ABT494 or ABT-494 or 4RA0KN46E0 or 1310726-60-3).af.	958
8	adalimumab/	38156
9	(Adalimumab* or adalimumab-adaz or adalimumab-adbm or adalimumab-afzb or adalimumab-atto or adalimumab-bwwd or Hadlima* or Humira* or Imraldi* or Amjevita* or Cyltezo* or Trudexa* or abp-501 or ABP 501 or bcd-057 or bi-695501 or bi695501 or chs-1420 or d2e7 or gp-2017 or gp2017 or lu-200134 or lu200134 or m-923 or m923 or msb-11022 or msb11022 or ons-3010 or sb-5 or sb5 or fys6t7f842 or FYS6T7F842 or 331731-18-1).af.	39453
10	certolizumab pegol/	7652
11	(Certolizumab* or Cimzia* or CDP 870 or CDP-870 or CDP870 or PHA-738144 or pha 738144 or pha738144 or UMD07X179E or 428863-50-7).af.	8370
12	etanercept/	33963
13	(Etanercept* or etanercept-szzs or etanercept-ykro or Recombinant human TNF or rhu TNFR:Fc or rhu-TNFR:Fc or TNFR-Immunoadhesin or TNFR Fc or "tnr 001" or tnr001 or Brenzys* or benepali* or Enbrel* or embrel* or Erelzi* or Davictrel* or	36009

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	Tunex* or altebrel* or CHS-0214 or DWP-422 or ENIA-11 or GP-2015 or GP2015 or GP2015C or HD-203 or HD203 or LBEC-0101 or LBEC0101 or SB-4 or SB4 or enia 11 or enia11 or OP401G7OJC or 185243-69-0 or 200013-86-1 or 2055118-96-0).af.	
14	golimumab/	8181
15	(Golimumab* or Simponi* or CNTO 148 or CNTO-148 or 91X1KLU43E or 476181-74-5).af.	8383
16	infliximab/	55254
17	(infliximab* or Infliximab-abda or Infliximab-axxq or Infliximab-dyyb or Infliximab-qbtx or Avsola* or Flixabi* or Inflectra* or Avsola* or avakine* or INFLIX* or ixifi* or Remicade* or Remsima* or Renflexis* or revellex* or zessly* or ABP 710 or ABP-710 or BOW-015 or BOW015 or CT-P-13 or CT-P13 or GP 1111 or GP-1111 or PF-06438179 or "PF 06438179" or pf 6438179 or pf06438179 or pf6438179 or TA-650 or SB2 or B72HH48FLU or 170277-31-3).af.	57204
18	ixekizumab/	2445
19	(Ixekizumab* or taltz* or LY 2439821 or LY-2439821 or LY2439821 or BTY153760O or 1143503-69-8).af.	2546
20	tofacitinib/	6108
21	(Tofacitinib* or Tasocitinib* or Tofacitinibum* or Xeljanz* or CP 690550 or CP- 690 550 or CP-690 or CP-690-550 or CP-690,550 or CP-690550 or CP690,550 or CP690550 or cp690550 10 or cp690550-10 or 87LA6FU830 or 477600-75-2 or 540737-29-9).af.	6605
22	secukinumab/	5023
23	(secukinumab* or Cosentyx* or AIN-457 or AIN457 or AIN457A or DLG4EML025 or 1229022-83-6 or 875356-43-7 or 875356-44-8).af.	5225
24	filgotinib/	666
25	(filgotinib* or g 146034 or g 146034-101 or g146034 or g146034-101 or "glpg 0634" or glpg0634 or GS-6034 or 3XVL385Q0M or 1206161-97-8 or 1540859-07-1).af.	720
26	bimekizumab/	202
27	(Bimekizumab* or UCB4940 or 09495UIM6V or 1418205-77-2).af.	212
28	(Hulio* or Imraldi* or Hefiya* or Amgevita* or Idacio* or Hyrimoz* or Halimatoz* or Amsparity* or Erelzi* or Benepali* or Zessly* or Flixabi*).af.	349
29	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	94654
30	exp economic evaluation/	325087
31	health-economics/	33754
32	exp health-care-cost/	309369
33	exp pharmacoeconomics/	213779
34	(economic* or cost or costs or costly or costing or expense or expenses or price or prices or pricing or pharmacoeconomic* or CEA or CUA or CBA or CMA).ti,ab,kw.	1264209
35	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kw.	287123
36	(expenditure* not energy).ti,ab,kw.	44630
37	(value adj1 money).ti,ab,kw.	38
38	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	278427
39	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	1987778
40	(ankylosing spondylitis quality of life or ASQoL).ti,ab,kw.	628
41	(visual analog* scale or VAS).ti,ab,kw.	124112
42	(Multidimensional Fatigue Inventory or MFI).ti,ab,kw.	10792
43	((Work Productivity and Activity Index) or WPAI or WPAI-SpA).ti,ab,kw.	1834
44	(Health Assessment Questionnaire or HAQ).ti,ab,kw.	14477
45	("HAQ for Spondyloarthropathies" or HAQ-S).ti,ab,kw.	148
46	("Medical Outcomes Study" or MOS).ti,ab,kw.	23456
47	("Patient Global Assessment" or PGA).ti,ab,kw.	10406
48	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47	179185
49	(15D or 15-D or 15 dimension).ti,ab,kw.	7100
50	(eq-5d or eq5d or eq-5 or eq5 or EQ-5D-Y or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or	27036

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	euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro* quality of life or european qol or EQ-5D-3L).ti,ab,ot,hw,kw.	
51	(sf6 or sf 6 or SF-6D or short form 6 or short-form 6 or short-form six or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot,hw,kw.	4053
52	(sf10 or sf 10 or short form 10 or short-form 10 or short-form ten or shortform 10 or sf ten or sften or shortform ten or short form ten).ti,ab,ot,hw,kw.	229
53	(sf12 or sf 12 or short form 12 or short-form 12 or short-form twelve or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab,ot,hw,kw.	12656
54	(sf16 or sf 16 or short form 16 or short-form 16 or short-form sixteen or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,ot,hw,kw.	66
55	(sf20 or sf 20 or short form 20 or short-form 20 or short-form twenty or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab,ot,hw,kw.	532
56	(sf36 or sf 36 or short form 36 or short-form 36 or short-form thirty six or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot,hw,kw.	53221
57	(health utilities index$ or (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)).ti,ab,ot,hw,kw.	3919
58	("time trade off" or "time tradeoff" or "time trade-off" or TTO).ti,ab,ot,hw,kw.	3056
59	(standard gamble$ or SG).ti,ab,ot,hw,kw.	18269
60	("discrete choice" or DCE).ti,ab,ot,hw,kw.	12181
61	(AQoL or "Assessment of Quality of Life").ti,ab,ot,hw,kw.	3411
62	Quality-Adjusted Life Years/	30043
63	(HRQoL or HRQL or HQL or QoL or (quality adj3 life) or HYE or HYES).ti,ab,ot,hw,kw.	683203
64	"quality of life"/	527870
65	socioeconomics/	148637
66	uncertainty/	38172
67	(uncertain* or wellbeing or "well being" or rosser or "willingness to pay").ti,ab,kw.	389957
68	Utility*.ti,ab,kw.	313955
69	(illness state*1 or health state* or health status or Quality adjusted life year* or QALY or QALD or qale or qtime or life year$ or ICER or "incremental cost").ti,ab,ot,hw,kw.	225798
70	(burden and (disease or illness or caregiver or home)).tw.	178635
71	(lost adj2 (productivity or work or employment or earnings)).ti,ab,kw.	4629
72	49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71	1777701
73	48 or 72	1913028
74	39 or 73	3572645
75	5 and 29 and 74	2287
76	(conference abstract or conference review).pt.	4243990
77	75 not 76	1065
78	limit 77 to dc=20210324-20211028	66

Table 25. Ovid MEDLINE(R) ALL: 1946 to October 27, 2021 (Searched: 28.10.21)

1	Spondylitis, Ankylosing/	15442
2	((Ankyl* or Axial*) adj2 (spondyl* or spine or spinal or verteb*)).ti,ab,kw,ot,kf.	18628
3	(axial SpA or axSpA or nr-axSpA or SpA).ti,ab,kw,ot,kf.	12920
4	(Bechterew* or bekhterev* or marie stru?mpell* or marie-struempell* or "Strumpell–Marie disease" or (Marie* adj disease) or (Pierre Marie* adj disease)).ti,ab,kw,ot,kf.	896
5	1 or 2 or 3 or 4	33345
6	(Upadacitinib* or Rinvoq* or ABT 494 or ABT494 or ABT-494 or 4RA0KN46E0 or 1310726-60-3).af.	240
7	Adalimumab/	6071
8	(Adalimumab* or adalimumab-adaz or adalimumab-adbm or adalimumab-afzb or adalimumab-atto or adalimumab-bwwd or Hadlima* or Humira* or Imraldi* or	10051

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	Amjevita* or Cyltezo* or Trudexa* or abp-501 or ABP 501 or bcd-057 or bi-695501 or bi695501 or chs-1420 or d2e7 or gp-2017 or gp2017 or lu-200134 or lu200134 or m-923 or m923 or msb-11022 or msb11022 or ons-3010 or sb-5 or sb5 or fys6t7f842 or FYS6T7F842 or 331731-18-1).af.	
9	Certolizumab Pegol/	677
10	(Certolizumab* or Cimzia* or CDP 870 or CDP-870 or CDP870 or PHA-738144 or pha 738144 or pha738144 or UMD07X179E or 428863-50-7).af.	1458
11	Etanercept/	6160
12	(Etanercept* or etanercept-szzs or etanercept-ykro or Recombinant human TNF or "rhu TNFR:Fc" or "rhu-TNFR:Fc" or TNFR-Immunoadhesin or TNFR Fc or "tnr 001" or tnr001 or Brenzys* or benepali* or Enbrel* or embrel* or Erelzi* or Davictrel* or Tunex* or altebrel* or CHS-0214 or DWP-422 or ENIA-11 or GP-2015 or GP2015 or GP2015C or HD-203 or HD203 or LBEC-0101 or LBEC0101 or SB-4 or SB4 or enia 11 or enia11 or OP401G7OJC or 185243-69-0 or 200013-86-1 or 2055118-96-0).af.	9926
13	(Golimumab* or Simponi* or CNTO 148 or CNTO-148 or 91X1KLU43E or 476181-74-5).af.	1426
14	Infliximab/	11091
15	(infliximab* or Infliximab-abda or Infliximab-axxq or Infliximab-dyyb or Infliximab-qbtx or Avsola* or Flixabi* or Inflectra* or Avsola* or avakine* or INFLIX* or ixifi* or Remicade* or Remsima* or Renflexis* or revellex* or zessly* or ABP 710 or ABP-710 or BOW-015 or BOW015 or CT-P-13 or CT-P13 or GP 1111 or GP-1111 or PF-06438179 or "PF 06438179" or pf 6438179 or pf06438179 or pf6438179 or TA-650 or SB2 or B72HH48FLU or 170277-31-3).af.	16661
16	(Ixekizumab* or taltz* or LY 2439821 or LY-2439821 or LY2439821 or BTY153760O or 1143503-69-8).af.	759
17	(Tofacitinib* or Tasocitinib* or Tofacitinibum* or Xeljanz* or CP 690550 or CP- 690 550 or CP-690 or CP-690-550 or CP-690,550 or CP-690550 or CP690,550 or CP690550 or cp690550 10 or cp690550-10 or 87LA6FU830 or 477600-75-2 or 540737-29-9).af.	2037
18	(secukinumab* or Cosentyx* or AIN-457 or AIN457 or AIN457A or DLG4EML025 or 1229022-83-6 or 875356-43-7 or 875356-44-8).af.	1500
19	(filgotinib* or g 146034 or g 146034-101 or g146034 or g146034-101 or "glpg 0634" or glpg0634 or GS-6034 or 3XVL385Q0M or 1206161-97-8 or 1540859-07-1).af.	170
20	(Bimekizumab* or UCB4940 or 09495UIM6V or 1418205-77-2).af.	65
21	(Hulio or Imraldi or Hefiya or Amgevita or Idacio or Hyrimoz or Halimatoz or Amsparity or Erelzi or Benepali or Zessly or Flixabi).af.	79
22	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	31318
23	economics/	27381
24	exp "Costs and Cost Analysis"/	250872
25	economics, dental/	1920
26	exp Economics, Hospital/ or Financial management, hospital/	32634
27	Economics, Medical/	9166
28	economics, nursing/	4007
29	economics, pharmaceutical/	3030
30	(economic* or cost or costs or costly or costing or expense or expenses or price or prices or pricing or pharmacoeconomic* or CEA or CUA or CBA or CMA).ti,ab,kw.	981490
31	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab.	213759
32	(expenditure* not energy).ti,ab.	32879
33	(value adj1 money).ti,ab.	36
34	(budget* or fiscal or funding or financial or finance*).ti,ab.	198897
35	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	1388786
36	(ankylosing spondylitis quality of life or ASQoL).ti,ab,kw.	214
37	(visual analog* scale or VAS).ti,ab,kw.	80952
38	(Disease Activity Score or ASDAS).ti,ab,kw.	5723
39	(Multidimensional Fatigue Inventory or MFI).ti,ab,kw.	4110

- ◊ Clarification questions

40	((Work Productivity and Activity Index) or WPAI or WPAI-SpA).ti,ab,kw.	418
41	(Health Assessment Questionnaire or HAQ).ti,ab,kw.	5458
42	("HAQ for Spondyloarthropathies" or HAQ-S).ti,ab,kw.	59
43	("Medical Outcomes Study" or MOS).ti,ab,kw.	12091
44	("Patient Global Assessment" or PGA).ti,ab,kw.	6238
45	36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	111412
46	(15D or 15-D or 15 dimension).ti,ab,kw.	5664
47	(eq-5d or eq5d or eq-5 or eq5 or EQ-5D-Y or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol or EQ-5D-3L).ti,ab,ot,hw,kw.	13906
48	(sf6 or sf 6 or SF-6D or short form 6 or short-form 6 or short-form six or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot,hw,kw.	3078
49	(sf10 or sf 10 or short form 10 or short-form 10 or short-form ten or shortform 10 or sf ten or sften or shortform ten or short form ten).ti,ab,ot,hw,kw.	145
50	(sf12 or sf 12 or short form 12 or short-form 12 or short-form twelve or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab,ot,hw,kw.	6637
51	(sf16 or sf 16 or short form 16 or short-form 16 or short-form sixteen or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,ot,hw,kw.	35
52	(sf20 or sf 20 or short form 20 or short-form 20 or short-form twenty or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab,ot,hw,kw.	420
53	(sf36 or sf 36 or short form 36 or short-form 36 or short-form thirty six or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot,hw,kw.	27894
54	(health utilities index$ or (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)).ti,ab,ot,hw,kw.	2006
55	("time trade off" or "time tradeoff" or "time trade-off" or TTO).ti,ab,ot,hw,kw.	2047
56	(standard gamble$ or SG).ti,ab,ot,hw,kw.	12211
57	("discrete choice" or DCE).ti,ab,ot,hw,kw.	8273
58	(AQoL or "Assessment of Quality of Life").ti,ab,ot,hw,kw.	2081
59	Quality-Adjusted Life Years/	13960
60	(HRQoL or HRQL or HQL or QoL or (quality adj3 life) or HYE or HYES).ti,ab,ot,hw,kw.	393126
61	quality of life/	224787
62	value of life/	5767
63	uncertainty/	14822
64	(uncertain$ or wellbeing or "well being" or rosser or "willingness to pay").tw.	301361
65	utilit$.ti,ab,kw.	233289
66	(illness state$1 or health state$ or health status or Quality adjusted life year$ or QALY or QALD or qale or qtime or life year$ or ICER or "incremental cost").ti,ab,ot,hw,kw.	199245
67	(burden and (disease or illness or caregiver or home)).tw.	109039
68	(lost adj2 (productivity or work or employment or earnings)).ti,ab,kw.	3147
69	46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68	1139727
70	45 or 69	1226946
71	35 or 70	2427054
72	5 and 22 and 71	658
73	limit 72 to dt=20210324-20211028	22

Table 26. Econlit <1886 to December 30, 2021>

1	(Axial spondyloarthritis or axSpA or ankylosing spondylitis).ti,ab.	4
2	limit 1 to yr="2021 -Current"	0
Number of results: 0		

- ◊ Clarification questions

Appendix C

Database: MEDLINE

Host: Ovid

Data Parameters: 1946 to January 14, 2022

Date of search: 17 Jan 2022

Table 27. Search strategy: MEDLINE

#	Searches	Results
1	Spondylitis, Ankylosing/	15608
2	((Ankyl* or Axial*) adj2 (spondyl* or spine or spinal or verteb*)).ti,ab,kw,ot,kf.	18889
3	(axial SpA or axSpA or nr-axSpA or SpA).ti,ab,kw,ot,kf.	13131
4	(Bechterew* or bekhterev* or marie stru?mpell* or marie-struempell* or "Strumpell–Marie disease" or (Marie* adj disease) or (Pierre Marie* adj disease)).ti,ab,kw,ot,kf.	896
5	1 or 2 or 3 or 4	33743
6	(Kromeya or Solymbic or Yuflyma or PF-06410293).af.	15
7	5 and 6	0
8	(Nepexto or BX2922 or Etacept or Etanar or GP2013 or PRX-106 or Yisaipu or Eticovo or Lifmior).af.	33
9	5 and 8	7
10	Etanercept/	6220
11	(Etanercept* or etanercept-szzs or etanercept-ykro or Recombinant human TNF or "rhu TNFR:Fc" or "rhu-TNFR:Fc" or TNFR-Immunoadhesin or TNFR Fc or "tnr 001" or tnr001 or Brenzys* or benepali* or Enbrel* or embrel* or Erelzi* or Davictrel* or Tunex* or altebrel* or CHS-0214 or DWP-422 or ENIA-11 or GP-2015 or GP2015 or GP2015C or HD-203 or HD203 or LBEC-0101 or LBEC0101 or SB-4 or SB4 or enia 11 or enia11 or OP401G7OJC or 185243-69-0 or 200013-86-1 or 2055118-96-0).af.	10015
12	10 or 11	10015
13	5 and 12	1068
14	9 or 13	1070
15	14 not 13	2

Database: Embase
Host: Ovid
Data Parameters: 1980 to 2022 Week 02
Date of search: 17 Jan 2022

Table 28. Search strategy: Embase

	Searches	Results
1	spondylarthritis/	9858
2	((Ankyl* or Axial*) adj2 (spondyl* or spine or spinal or verteb*)).ti,ab,kw,ot.	28763
3	(axial SpA or axSpA or nr-axSpA or SpA).ti,ab,kw,ot.	20780
4	(Bechterew* or bekhterev* or marie stru?mpell* or marie-struempell* or "Strumpell–Marie disease" or (Marie* adj disease) or (Pierre Marie* adj disease)).ti,ab,kw,ot.	718
5	1 or 2 or 3 or 4	47351
6	(Kromeya or Solymbic or Yuflyma or PF-06410293).af.	65

- ◊ Clarification questions

7	5 and 6	5
8	adalimumab/	38949
9	(Adalimumab* or adalimumab-adaz or adalimumab-adbm or adalimumab-afzb or adalimumab-atto or adalimumab-bwwd or Hadlima* or Humira* or Imraldi* or Amjevita* or Cyltezo* or Trudexa* or abp-501 or ABP 501 or bcd-057 or bi-695501 or bi695501 or chs-1420 or d2e7 or gp-2017 or gp2017 or lu-200134 or lu200134 or m-923 or m923 or msb-11022 or msb11022 or ons-3010 or sb-5 or sb5 or fys6t7f842 or FYS6T7F842 or 331731-18-1).af.	40295
10	8 or 9	40295
11	5 and 10	3594
12	7 or 11	3594
13	(Nepexto or BX2922 or Etacept or Etanar or GP2013 or PRX-106 or Yisaipu or Eticovo or Lifmior).af.	116
14	5 and 13	23
15	etanercept/	34362
16	(Etanercept* or etanercept-szzs or etanercept-ykro or Recombinant human TNF or rhu TNFR:Fc or rhu-TNFR:Fc or TNFR-Immunoadhesin or TNFR Fc or "tnr 001" or tnr001 or Brenzys* or benepali* or Enbrel* or embrel* or Erelzi* or Davictrel* or Tunex* or altebrel* or CHS-0214 or DWP-422 or ENIA-11 or GP-2015 or GP2015 or GP2015C or HD-203 or HD203 or LBEC-0101 or LBEC0101 or SB-4 or SB4 or enia 11 or enia11 or OP401G7OJC or 185243-69-0 or 200013-86-1 or 2055118-96-0).af.	36422
17	15 or 16	36422
18	5 and 17	3731
19	14 or 18	3734
20	19 not 18	3

◊ Clarification questions

Appendix D

Binary Outcomes (ASAS20, ASAS40, ASASPR, BASDAI50)

General Code

Data Preparation

```
## NMA selection and data prep

### USE NMA NUMBER 5 to replicate naive results displayed in Document B
### USE NMA NUMBER 8 to replicate bio-IR results displayed in Document B

### NMA 1, 2, 3, 4, 5, and 6 utilize the naive data set (worksheet 'naive'
of 'AS_NMA_R_final_data_inputs_naive_bio_IR_v1.0') as the 'final_data'
### NMA 7 and 8 utilize the bio-IR data set (worksheet 'bio_IR' of
'AS_NMA_R_final_data_inputs_naive_bio_IR_v1.0') as the 'final_data'
nma.select <- function() {

 ## NMA selection ##

 # Primary NMA (naive)
 ifelse (nma.number == 1,
      nma_data_pre <- final_data %>%
       filter(!(Study == "SELECT_AXIS_1" & Week_outcome_1 == 14)) %>%
       filter(!(substr(Study, start=11, stop=15)=="naive")),

      ifelse (nma.number == 2,
           nma_data_pre <- final_data %>%
            filter(!(Study == "SELECT_AXIS_1" & Week_outcome_1 == 12)) %>%
            filter(!(substr(Study, start=11, stop=15)=="naive")),

           ifelse (nma.number == 3,
                nma_data_pre <- final_data %>%
                 filter(Week_outcome_1 == 12) %>%
                 filter(!(substr(Study, start=11, stop=15)=="naive")),

                # Secondary NMA 2 (naive)
                ifelse (nma.number == 4,
                     nma_data_pre <- final_data %>%
                      filter(!(Study == "SELECT_AXIS_1" & Week_outcome_1 == 14))
%>%
                      filter(PriorBiologic_BL_p == 0),

                     # Secondary NMA 3 (naive)
                     ifelse (nma.number == 5,
                          nma_data_pre <- final_data %>%
                           filter(!(Study == "SELECT_AXIS_1" & Week_outcome_1 ==
```

- ◊ Clarification questions

```
12)) %>%
                                filter(PriorBiologic_BL_p == 0),

                              ifelse (nma.number == 6,
                                   nma_data_pre <- final_data %>%
                                    filter(Week_outcome_1 == 12) %>%
                                    filter(PriorBiologic_BL_p == 0),

                                   # Primary NMA 4 (bio-IR)
                                   ifelse (nma.number == 7,
                                         nma_data_pre <- final_data %>%
                                          filter(!(Study == 'SELECT_AXIS_2' &
Week_outcome_1 == 14)),

                                        # Secondary NMA 5 (bio-IR)
                                        ifelse (nma.number == 8,
                                              nma_data_pre <- final_data %>%
                                               filter(!(Study == 'SELECT_AXIS_2' &
Week_outcome_1 == 12)),

                                   print("Number not valid")

                              ))))))))

 ifelse (nma.endpt == "BASDAI50",

      nma_data <- nma_data_pre %>%
       filter(!is.na(BASDAI50_1_n)) %>%
       mutate(
        sampleSize = round(as.numeric(BASDAI50_1_bigN),0),
        treatment = Treatment_arm,
        study = Study,
        responders = round(as.numeric(BASDAI50_1_n),0)
       ) %>%
       select(study, treatment, sampleSize, responders),

      ifelse (nma.endpt == "ASAS20",

           nma_data <- nma_data_pre %>%
            filter(!is.na(ASAS20_1_n)) %>%
            mutate(
             sampleSize = round(as.numeric(ASAS20_1_bigN),0),
             treatment = Treatment_arm,
             study = Study,
             responders = round(as.numeric(ASAS20_1_n),0)
            ) %>%
            select(study, treatment, sampleSize, responders),

           ifelse (nma.endpt == "ASAS40",
```

◊ Clarification questions

```
    nma_data <- nma_data_pre %>%
     filter(!is.na(ASAS40_1_n)) %>%
     mutate(
      sampleSize = round(as.numeric(ASAS40_1_bigN),0),
      treatment = Treatment_arm,
      study = Study,
      responders = round(as.numeric(ASAS40_1_n),0)
     ) %>%
     select(study, treatment, sampleSize, responders),

    ifelse (nma.endpt == "ASASPR",

        nma_data <- nma_data_pre %>%
         filter(!is.na(ASASPR_1_n)) %>%
         mutate(
          sampleSize = round(as.numeric(ASASPR_1_bigN),0),
          treatment = Treatment_arm,
          study = Study,
          responders = round(as.numeric(ASASPR_1_n),0)
         ) %>%
         select(study, treatment, sampleSize, responders),

        print("Outcome not valid")

    ))))

## BNMA data prep

bugs_data <- nma_data

# global copy
bugs_data_global_copy <<- bugs_data

# PBO receives ID=1
bugs_data$treatment[bugs_data$treatment =="PBO"] <- "1PBO"

# Number of treatment arms in each study (na)
bugs_data <- bugs_data %>% group_by(study) %>% mutate(na = n())
max_na <- max(bugs_data$na)

# Order by treatment
bugs_data <- bugs_data[order(bugs_data$treatment),]

# Assign ID to each unique treatment arm (t)
bugs_data$t <- with(bugs_data, ave(as.character(treatment), FUN=function(x)
match(x, unique(x))))
bugs_data$t <- as.integer(bugs_data$t)
bugs_data$treatment[bugs_data$treatment =="1PBO"] <- "PBO"
```

- ◊ Clarification questions

```
# Get the mapping of treatment ID and treatment labels

bugs_trt.key <- cbind(bugs_data$treatment, bugs_data$t)
bugs_trt.key <- data.frame(unique(bugs_trt.key, incomparables = FALSE))

colnames(bugs_trt.key) <- c("Treat.order", "Treat_id")

assign("Trt.key", bugs_trt.key, envir= .GlobalEnv)

Treat.order <<- Trt.key$Treat.order

# The data needs to be order by study
bugs_data <- bugs_data[order(bugs_data$study, bugs_data$t), ]

# Assign ID to each study
bugs_data$Study <- with(bugs_data, ave(as.character(study), FUN=function(x)
match(x, unique(x))))

study <<-  (bugs_data$study)
Study <<- as.integer(bugs_data$Study)
Treat <<- bugs_data$treatment
nTreat <<- bugs_data$t

N <<- as.numeric(bugs_data$sampleSize)
Outcomes <<- bugs_data$responders

bugs_data <- bugs_data[order(bugs_data$study, bugs_data$t ),]

#Number of unique treatments
nt <<- max(bugs_data$t)

# Number of treatment arms in each study (arm_id)
bugs_data <- bugs_data %>% dplyr::group_by(study) %>%  dplyr::mutate(arm_id =
dplyr::row_number())

# Rename sampleSize (n) and responders (r)
bugs_data <- bugs_data %>% dplyr::rename(n=sampleSize)
bugs_data <- bugs_data %>% dplyr::rename(r=responders)

# Reshape the data to have one row per study
bugs_data <- reshape2::melt(bugs_data, id.var = c("study", "arm_id"))
bugs_data <- reshape::cast(bugs_data, study~variable + arm_id)

# Remove "_" from the names of newly generated variables
names(bugs_data)[-1] <- sub("_", "", names(bugs_data)[-1])

n_col <- ncol(bugs_data)


if (max_na == 4) {
```

- ◊ Clarification questions

```
  # Change some variable type to numeric
  name_cols <- names(bugs_data)[6:n_col]
  bugs_data[6:n_col] <- lapply(bugs_data[name_cols], as.numeric)

  # OpenBUGS data
  bugs_data <- bugs_data[order(bugs_data$t2, bugs_data$t3, bugs_data$t4),]

  na <- bugs_data$na1
  t <- cbind(bugs_data$t1, bugs_data$t2, bugs_data$t3, bugs_data$t4)
  r <- cbind(bugs_data$r1, bugs_data$r2, bugs_data$r3, bugs_data$r4)
  n <- cbind(bugs_data$n1, bugs_data$n2, bugs_data$n3, bugs_data$n4)

} else if (max_na == 3) {
  # Change some variable type to numeric
  name_cols <- names(bugs_data)[5:n_col]
  bugs_data[5:n_col] <- lapply(bugs_data[name_cols], as.numeric)

  # OpenBUGS data
  bugs_data <- bugs_data[order(bugs_data$t2, bugs_data$t3),]

  na <- bugs_data$na1
  t <- cbind(bugs_data$t1, bugs_data$t2, bugs_data$t3)
  r <- cbind(bugs_data$r1, bugs_data$r2, bugs_data$r3)
  n <- cbind(bugs_data$n1, bugs_data$n2, bugs_data$n3)

} else if (max_na == 2) {
  # Change some variable type to numeric
  name_cols <- names(bugs_data)[4:n_col]
  bugs_data[4:n_col] <- lapply(bugs_data[name_cols], as.numeric)

  # OpenBUGS data
  bugs_data <<- bugs_data[order(bugs_data$t2),]

  na <- bugs_data$na1
  t <- cbind(bugs_data$t1, bugs_data$t2)
  r <- cbind(bugs_data$r1, bugs_data$r2)
  n <- cbind(bugs_data$n1, bugs_data$n2)

}

study <- bugs_data$study
ns <- nrow(bugs_data) # Number of studies

# Calculate the average log of odds for the PBO
odds_pbo <<- bugs_data$r1 / (bugs_data$n1 - bugs_data$r1)

# Following NICE DSU example: replace odds == 0 with 0.01 prior
calculating the log of odds

odds_pbo[odds_pbo == 0] <- 0.01
```

- Clarification questions

```
 lodds <- log(odds_pbo)
 mx <<- mean(lodds)
 vx <- var(lodds)
 meanA <<- mx
 precA <<- 1 / vx

 # Export to global environment
 data <-
  list(
   ns = ns,
   nt = nt,
   na = na,
   t = t,
   r = r,
   n = n,
   mx = mx,
   meanA = meanA,
   precA = precA,
   mx_bl = mx
  )

 nma.data.sup <<- data

 bnma_prepdata <<- list(Outcomes, Treat, N, Study, Treat.order)

}
```

NMA Run via BNMA

```
## BNMA model function for binary outcomes (consistency model) ##

bnma.binary_main <- function(type, baseline_bnma,
                  hy.prior.bl_dist="dunif", hy.prior.bl_a=0, hy.prior.bl_b=5,
                  hy.prior.Eta_dist="dunif", hy.prior.Eta_a=0, hy.prior.Eta_b=5,
                  seed=rsd, RNG.inits=jags_seed) {

 network <<- with(bnma_prepdata, network.data(
  Outcomes = Outcomes,
  Study = study,
  Treat = Treat,
  N = N,
  SE = NULL, #Use only when response=normal
  response = "binomial",
  Treat.order = Treat.order,
  type = type,
  rank.preference = "higher", #Events are good
  # Covariate adjustment and effect
  covariate = NULL,
  covariate.type = NULL,
  covariate.model = NULL,
```

- ◊ Clarification questions

```
  mean.cov = NULL,
  prec.cov = NULL,
  hy.prior.cov = NULL, #For exchangeable only
  # Relative effect
  mean.d = mean.prior,
  prec.d = prec.prior,
  # Study effect (baseline risk)
  baseline.risk = baseline.risk, #Exchangeable, independent
  mean.Eta = mean.prior,
  prec.Eta = prec.prior,
  hy.prior.Eta = list(hy.prior.Eta_dist, hy.prior.Eta_a, hy.prior.Eta_b), #For
exchangeable only
  # Baseline slope
  baseline = baseline_bnma, #Common, exchangeable, independent, none
  mean.bl = mean.prior,
  prec.bl = prec.prior,
  hy.prior.bl = list(hy.prior.bl_dist, hy.prior.bl_a, hy.prior.bl_b), #For exchangeable
only
  # Prior for the heterogeneity parameter (supports uniform, gamma, and
half normal)
  hy.prior = list(hy.prior_dist, hy.prior_a, hy.prior_b),
  # Standard treatment effect
  mean.A = meanA,
  prec.A = precA))

 set.seed(seed)

 result <- network.run(network,
              inits = NULL,
              n.chains = 3,
              max.run = 1e+05,
              setsize = setsize,
              n.run = run,
              conv.limit = 1.05,
              extra.pars.save = NULL,
              RNG.inits = RNG.inits)
}
```

UME NMA Run via BNMA

```
## BNMA model function for binary outcomes (unrelated mean effects) ##

bnma.binary_ume <- function(type) {

 network_ume <- with(bnma_prepdata, ume.network.data(
  Outcomes = Outcomes,
  Study = Study,
  Treat = nTreat,
  N = N,
  SE = NULL, #Use only when response=normal
```

- ◊ Clarification questions

```
  response = "binomial",
  type = type,
  mean.mu = 0,
  prec.mu = .0001,
  mean.d = 0,
  prec.d = .0001,
  hy.prior = list(hy.prior_dist, hy.prior_a, hy.prior_b),
  dic = T))

 result_ume <<- ume.network.run(network_ume,
                  inits = NULL,
                  n.chains = 3,
                  max.run = 1e+05,
                  setsize = setsize,
                  n.run = run,
                  conv.limit = 1.05,
                  extra.pars.save = NULL)
}
```

Selected Model Code for Results Presented in Section B.3.9.2 and associated UME models - bDMARD-naïve

ASAS40 - Random Effects (RE)

NMA Run via BNMA Inputs

```
# Specifications
 nma.endpt <- "ASAS40"
 nma.number <- 5 #UPA: 14 weeks; Comparators: 12-16 weeks; Mixed bDMARD-exposure: Excluded
 run <- 100000
 setsize <- 10000
 baseline <- "common"
 baseline.risk <- "independent"
 hy.prior_dist <- "dunif"
 hy.prior_a <- 0
 hy.prior_b <- 5
 mean.prior <- 0
 prec.prior <- .0001

# NMA run
 bnma.binary_main(type="random", baseline_bnma="none")
 bnma.binary_ume(type="random")
```

Produced Primary Model Code

```
## model
## {
##  for (i in 1:14) {
```

- Clarification questions

```
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
##  }
##  for (i in 1:14) {
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        r[i,k] ~ dbin(p[i,k],n[i,k])
##        logit(p[i,k]) <- Eta[i] + delta[i,k]
##        rhat[i,k] <- p[i,k] * n[i,k]
##        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k])*(log(n[i,k]-r[i,k]) -
log(n[i,k]-rhat[i,k])))
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for(k in 2:na[i]){
##        delta[i,k] ~ dnorm(md[i,k],precd[i,k])
##        md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
##        precd[i,k] <- prec *2*(k-1)/k
##        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
##        sw[i,k] <- sum(w[i,1:(k-1)])/(k-1)
##     }
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:12){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  sd ~ dunif(hy.prior.1, hy.prior.2)
##  prec <- pow(sd,-2)
##  logvar <- log(pow(sd, 2))
##  rank_number <- rank(d[])
##  for(k in 1:12){
##     rk[k] <- 12 +1- rank_number[k]
##     for(h in 1:12){ prob[h,k] <- equals(rk[k],h)}
##  }
##  A ~ dnorm(mean.A, prec.A)
##  for(k in 1:12) { logit(T[k]) <- A + d[k] }
##  for(k in 1:12) {
##     for(kk in (k+1):12) {
##     NNT[kk,k] <- 1/(T[kk] - T[k])
##     RD[kk,k] <- T[kk] - T[k]
##     RR[kk,k] <- T[kk]/T[k]
##     }
##  }
## }
```

Produced UME Model

```
## model
## {
##  for(i in 1:14) {
```

- Clarification questions

```
##     delta[i,1] <- 0
##     mu[i] ~ dnorm(mean.mu,prec.mu)
##     for(k in 1:na[i]) {
##        r[i,k] ~ dbin(p[i,k], n[i,k])
##        logit(p[i,k]) <- mu[i] + delta[i,k]
##        rhat[i,k] <- p[i,k] * n[i,k]
##        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])- log(rhat[i,k])) + (n[i,k] - r[i,k]) * (log(n[i,k] -
r[i,k]) - log(n[i,k] - rhat[i,k])))
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for (k in 2:na[i]) {
##        delta[i,k] ~ dnorm(d[t[i,1],t[i,k]], prec)
##     }
## }
## totresdev <- sum(resdev[])
## for(c in 1:11) {
##     for(k in (c+1):12) {
##        d[c,k] ~ dnorm(mean.d, prec.d)
##     }
## }
## sd ~ dunif(hy.prior.1, hy.prior.2)
## prec <- pow(sd,-2)
## }
```

ASAS40 - Random Effects with Baseline-risk Adjustment (REA)

NMA Run via BNMA Inputs

```
# Specifications
 nma.endpt <- "ASAS40"
 nma.number <- 5 #UPA: 14 weeks; Comparators: 12-16 weeks; Mixed bDMARD-
exposure: Excluded
 run <- 100000
 setsize <- 10000
 baseline <- "common"
 baseline.risk <- "independent"
 hy.prior_dist <- "dunif"
 hy.prior_a <- 0
 hy.prior_b <- 5
 mean.prior <- 0
 prec.prior <- .0001

# NMA run
 bnma.binary_main(type="random", baseline_bnma=baseline)
 bnma.binary_ume(type="random")
```

Produced Primary Model Code

```
## model
## {
```

- ◊ Clarification questions

```
##  for (i in 1:14) {
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
##  }
##  for (i in 1:14) {
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        r[i,k] ~ dbin(p[i,k],n[i,k])
##        logit(p[i,k]) <- Eta[i] + delta[i,k]
##        rhat[i,k] <- p[i,k] * n[i,k]
##        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k])*(log(n[i,k]-r[i,k]) -
log(n[i,k]-rhat[i,k])))
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for(k in 2:na[i]){
##        delta[i,k] ~ dnorm(md[i,k],precd[i,k])
##        md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] + (b_bl[t[i,k]] - b_bl[t[i,1]]) * (Eta[i] - mx_bl)
##        precd[i,k] <- prec *2*(k-1)/k
##        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) - (b_bl[t[i,k]] - b_bl[t[i,1]]) * (Eta[i] -
mx_bl)
##        sw[i,k] <- sum(w[i,1:(k-1)])/(k-1)
##     }
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:12){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  b_bl[1] <- 0
##  for(k in 2:12){
##     b_bl[k] <- B
##  }
##  B ~ dnorm(mean.bl, prec.bl)
##  sd ~ dunif(hy.prior.1, hy.prior.2)
##  prec <- pow(sd,-2)
##  logvar <- log(pow(sd, 2))
##  rank_number <- rank(d[])
##  for(k in 1:12){
##     rk[k] <- 12 +1- rank_number[k]
##     for(h in 1:12){ prob[h,k] <- equals(rk[k],h)}
##  }
##  A ~ dnorm(mean.A, prec.A)
##  for(k in 1:12) { logit(T[k]) <- A + d[k] }
##  for(k in 1:12) {
##     for(kk in (k+1):12) {
##     NNT[kk,k] <- 1/(T[kk] - T[k])
##     RD[kk,k] <- T[kk] - T[k]
##     RR[kk,k] <- T[kk]/T[k]
##     }
```

- Clarification questions

```
## }
## }
```

Produced UME Model

```
## model
## {
##  for(i in 1:14) {
##     delta[i,1] <- 0
##     mu[i] ~ dnorm(mean.mu,prec.mu)
##     for(k in 1:na[i]) {
##        r[i,k] ~ dbin(p[i,k], n[i,k])
##        logit(p[i,k]) <- mu[i] + delta[i,k]
##        rhat[i,k] <- p[i,k] * n[i,k]
##        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])- log(rhat[i,k])) + (n[i,k] - r[i,k]) * (log(n[i,k] -
r[i,k]) - log(n[i,k] - rhat[i,k])))
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for (k in 2:na[i]) {
##        delta[i,k] ~ dnorm(d[t[i,1],t[i,k]], prec)
##     }
##  }
##  totresdev <- sum(resdev[])
##  for(c in 1:11) {
##     for(k in (c+1):12) {
##        d[c,k] ~ dnorm(mean.d, prec.d)
##     }
##  }
##  sd ~ dunif(hy.prior.1, hy.prior.2)
##  prec <- pow(sd,-2)
## }
```

BASDAI50 - Random Effects (RE)

NMA Run via BNMA Inputs

```
# Specifications
 nma.endpt <- "BASDAI50"
 nma.number <- 5 #UPA: 14 weeks; Comparators: 12-16 weeks; Mixed bDMARD-
exposure: Excluded
 run <- 100000
 setsize <- 10000
 baseline <- "common"
 baseline.risk <- "independent"
 hy.prior_dist <- "dunif"
 hy.prior_a <- 0
 hy.prior_b <- 5
 mean.prior <- 0
 prec.prior <- .0001
```

- ◊ Clarification questions

```
# NMA run
 bnma.binary_main(type="random", baseline_bnma="none")
 bnma.binary_ume(type="random")
```

Produced Primary Model Code

```
## model
## {
##  for (i in 1:10) {
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
##  }
##  for (i in 1:10) {
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        r[i,k] ~ dbin(p[i,k],n[i,k])
##        logit(p[i,k]) <- Eta[i] + delta[i,k]
##        rhat[i,k] <- p[i,k] * n[i,k]
##        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k])*(log(n[i,k]-r[i,k]) -
log(n[i,k]-rhat[i,k])))
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for(k in 2:na[i]){
##        delta[i,k] ~ dnorm(md[i,k],precd[i,k])
##        md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
##        precd[i,k] <- prec *2*(k-1)/k
##        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
##        sw[i,k] <- sum(w[i,1:(k-1)])/(k-1)
##     }
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:10){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  sd ~ dunif(hy.prior.1, hy.prior.2)
##  prec <- pow(sd,-2)
##  logvar <- log(pow(sd, 2))
##  rank_number <- rank(d[])
##  for(k in 1:10){
##     rk[k] <- 10 +1- rank_number[k]
##     for(h in 1:10){ prob[h,k] <- equals(rk[k],h)}
##  }
##  A ~ dnorm(mean.A, prec.A)
##  for(k in 1:10) { logit(T[k]) <- A + d[k] }
##  for(k in 1:10) {
##     for(kk in (k+1):10) {
##     NNT[kk,k] <- 1/(T[kk] - T[k])
##     RD[kk,k] <- T[kk] - T[k]
##     RR[kk,k] <- T[kk]/T[k]
```

- ◊ Clarification questions

```
##     }
## }
## }
```

Produced UME Model

```
## model
## {
##  for(i in 1:10) {
##     delta[i,1] <- 0
##     mu[i] ~ dnorm(mean.mu,prec.mu)
##     for(k in 1:na[i]) {
##        r[i,k] ~ dbin(p[i,k], n[i,k])
##        logit(p[i,k]) <- mu[i] + delta[i,k]
##        rhat[i,k] <- p[i,k] * n[i,k]
##        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])- log(rhat[i,k])) + (n[i,k] - r[i,k]) * (log(n[i,k] -
r[i,k]) - log(n[i,k] - rhat[i,k])))
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for (k in 2:na[i]) {
##        delta[i,k] ~ dnorm(d[t[i,1],t[i,k]], prec)
##     }
##  }
##  totresdev <- sum(resdev[])
##  for(c in 1:9) {
##     for(k in (c+1):10) {
##        d[c,k] ~ dnorm(mean.d, prec.d)
##     }
##  }
##  sd ~ dunif(hy.prior.1, hy.prior.2)
##  prec <- pow(sd,-2)
## }
```

BASDAI50 - Random Effects with Baseline-risk Adjustment (REA)

NMA Run via BNMA Inputs

```
# Specifications
 nma.endpt <- "BASDAI50"
 nma.number <- 5 #UPA: 14 weeks; Comparators: 12-16 weeks; Mixed bDMARD-
exposure: Excluded
 run <- 100000
 setsize <- 10000
 baseline <- "common"
 baseline.risk <- "independent"
 hy.prior_dist <- "dunif"
 hy.prior_a <- 0
 hy.prior_b <- 5
 mean.prior <- 0
 prec.prior <- .0001
```

- ◊ Clarification questions

```
# NMA run
 bnma.binary_main(type="random", baseline_bnma=baseline)
 bnma.binary_ume(type="random")
```

Produced Primary Model Code

```
## model
## {
##  for (i in 1:10) {
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
##  }
##  for (i in 1:10) {
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        r[i,k] ~ dbin(p[i,k],n[i,k])
##        logit(p[i,k]) <- Eta[i] + delta[i,k]
##        rhat[i,k] <- p[i,k] * n[i,k]
##        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k])*(log(n[i,k]-r[i,k]) -
log(n[i,k]-rhat[i,k])))
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for(k in 2:na[i]){
##        delta[i,k] ~ dnorm(md[i,k],precd[i,k])
##        md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] + (b_bl[t[i,k]] - b_bl[t[i,1]]) * (Eta[i] - mx_bl)
##        precd[i,k] <- prec *2*(k-1)/k
##        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) - (b_bl[t[i,k]] - b_bl[t[i,1]]) * (Eta[i] -
mx_bl)
##        sw[i,k] <- sum(w[i,1:(k-1)])/(k-1)
##     }
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:10){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  b_bl[1] <- 0
##  for(k in 2:10){
##     b_bl[k] <- B
##  }
##  B ~ dnorm(mean.bl, prec.bl)
##  sd ~ dunif(hy.prior.1, hy.prior.2)
##  prec <- pow(sd,-2)
##  logvar <- log(pow(sd, 2))
##  rank_number <- rank(d[])
##  for(k in 1:10){
##     rk[k] <- 10 +1- rank_number[k]
##     for(h in 1:10){ prob[h,k] <- equals(rk[k],h)}
##  }
```

- ◊ Clarification questions

```
##  A ~ dnorm(mean.A, prec.A)
##  for(k in 1:10) { logit(T[k]) <- A + d[k] }
##  for(k in 1:10) {
##     for(kk in (k+1):10) {
##     NNT[kk,k] <- 1/(T[kk] - T[k])
##     RD[kk,k] <- T[kk] - T[k]
##     RR[kk,k] <- T[kk]/T[k]
##     }
##  }
## }
```

Produced UME Model

```
## model
## {
##  for(i in 1:10) {
##     delta[i,1] <- 0
##     mu[i] ~ dnorm(mean.mu,prec.mu)
##     for(k in 1:na[i]) {
##        r[i,k] ~ dbin(p[i,k], n[i,k])
##        logit(p[i,k]) <- mu[i] + delta[i,k]
##        rhat[i,k] <- p[i,k] * n[i,k]
##        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])- log(rhat[i,k])) + (n[i,k] - r[i,k]) * (log(n[i,k] -
r[i,k]) - log(n[i,k] - rhat[i,k])))
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for (k in 2:na[i]) {
##        delta[i,k] ~ dnorm(d[t[i,1],t[i,k]], prec)
##     }
##  }
##  totresdev <- sum(resdev[])
##  for(c in 1:9) {
##     for(k in (c+1):10) {
##        d[c,k] ~ dnorm(mean.d, prec.d)
##     }
##  }
##  sd ~ dunif(hy.prior.1, hy.prior.2)
##  prec <- pow(sd,-2)
## }
```

Selected Model Code for Results Presented in Section B.3.9.2 - bDMARD-IR

ASAS40 - Fixed Effects (FE)

NMA Run via BNMA Inputs

```
# Specifications
 nma.endpt <- "ASAS40"
```

- ◊ Clarification questions

```
nma.number <- 8 #UPA: 14 weeks; Comparators: 16 weeks; bio-IR
run <- 100000
setsize <- 10000
baseline <- "common"
baseline.risk <- "independent"
hy.prior_dist <- "dunif"
hy.prior_a <- 0
hy.prior_b <- 5
mean.prior <- 0
prec.prior <- .0001

# NMA run
bnma.binary_main(type="fixed", baseline_bnma="none")
```

Produced Primary Model Code

```
## model
## {
##  for (i in 1:2) {
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
##  }
##  for (i in 1:2) {
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        r[i,k] ~ dbin(p[i,k],n[i,k])
##        logit(p[i,k]) <- Eta[i] + d[t[i,k]] - d[t[i,1]]
##        rhat[i,k] <- p[i,k] * n[i,k]
##        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k])*(log(n[i,k]-r[i,k]) -
log(n[i,k]-rhat[i,k])))
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:4){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  rank_number <- rank(d[])
##  for(k in 1:4){
##     rk[k] <- 4 +1- rank_number[k]
##     for(h in 1:4){ prob[h,k] <- equals(rk[k],h)}
##  }
##  A ~ dnorm(mean.A, prec.A)
##  for(k in 1:4) { logit(T[k]) <- A + d[k] }
##  for(k in 1:4) {
##     for(kk in (k+1):4) {
##     RD[kk,k] <- T[kk] - T[k]
##     RR[kk,k] <- T[kk]/T[k]
##     }
```

- ◊ Clarification questions

```
## }
## }
```

BASDAI50 - Fixed Effects (FE)

NMA Run via BNMA Inputs

```
# Specifications
 nma.endpt <- "BASDAI50"
 nma.number <- 8 #UPA: 14 weeks; Comparators: 16 weeks; bio-IR
 run <- 100000
 setsize <- 10000
 baseline <- "common"
 baseline.risk <- "independent"
 hy.prior_dist <- "dunif"
 hy.prior_a <- 0
 hy.prior_b <- 5
 mean.prior <- 0
 prec.prior <- .0001

# NMA run
 bnma.binary_main(type="fixed", baseline_bnma="none")
```

Produced Primary Model Code

```
## model
## {
##  for (i in 1:2) {
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
##  }
##  for (i in 1:2) {
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        r[i,k] ~ dbin(p[i,k],n[i,k])
##        logit(p[i,k]) <- Eta[i] + d[t[i,k]] - d[t[i,1]]
##        rhat[i,k] <- p[i,k] * n[i,k]
##        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k])*(log(n[i,k]-r[i,k]) -
log(n[i,k]-rhat[i,k])))
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:4){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  rank_number <- rank(d[])
##  for(k in 1:4){
##     rk[k] <- 4 +1- rank_number[k]
```

- ◊ Clarification questions

```
##     for(h in 1:4){ prob[h,k] <- equals(rk[k],h)}
## }
## A ~ dnorm(mean.A, prec.A)
## for(k in 1:4) { logit(T[k]) <- A + d[k] }
## for(k in 1:4) {
##     for(kk in (k+1):4) {
##     RD[kk,k] <- T[kk] - T[k]
##     RR[kk,k] <- T[kk]/T[k]
##     }
## }
## }
```

Continuous Outcomes (BASAI CFB, BASFI CFB)

General Code

Data Preperation

```
## NMA selection and data prep

### USE NMA NUMBER 5 to replicate naive results displayed in Document B
### USE NMA NUMBER 8 to replicate bio-IR results displayed in Document B

### NMA 1, 2, 3, 4, 5, and 6 utilize the naive data set (worksheet 'naive'
of 'AS_NMA_R_final_data_inputs_naive_bio_IR_v1.0') as the 'final_data'
### NMA 7 and 8 utilize the bio-IR data set (worksheet 'bio_IR' of
'AS_NMA_R_final_data_inputs_naive_bio_IR_v1.0') as the 'final_data'
nma.select <- function() {

 ## NMA selection ##

 # Primary NMA (naive)
 ifelse (nma.number == 1,
      nma_data_pre <- final_data %>%
       filter(!(Study == "SELECT_AXIS_1" & Week_outcome_1 == 14)) %>%
       filter(!(substr(Study, start=11, stop=15)=="naive")),

      ifelse (nma.number == 2,
           nma_data_pre <- final_data %>%
            filter(!(Study == "SELECT_AXIS_1" & Week_outcome_1 == 12)) %>%
            filter(!(substr(Study, start=11, stop=15)=="naive")),

           ifelse (nma.number == 3,
                nma_data_pre <- final_data %>%
                 filter(Week_outcome_1 == 12) %>%
                 filter(!(substr(Study, start=11, stop=15)=="naive")),

                # Secondary NMA 2 (naive)
```

- ◊ Clarification questions

```
                ifelse (nma.number == 4,
                     nma_data_pre <- final_data %>%
                      filter(!(Study == "SELECT_AXIS_1" & Week_outcome_1 == 14)) %>%
                      filter(PriorBiologic_BL_p == 0),

                     # Secondary NMA 3 (naive)
                     ifelse (nma.number == 5,
                          nma_data_pre <- final_data %>%
                           filter(!(Study == "SELECT_AXIS_1" & Week_outcome_1 == 12)) %>%
                           filter(PriorBiologic_BL_p == 0),

                          ifelse (nma.number == 6,
                               nma_data_pre <- final_data %>%
                                filter(Week_outcome_1 == 12) %>%
                                filter(PriorBiologic_BL_p == 0),

                               # Primary NMA  bio-IR)
                                   ifelse (nma.number == 7,
                                     nma_data_pre <- final_data %>%
                                      filter(!(Study == 'SELECT_AXIS_2' & Week_outcome_1 == 14)),

                                     # Secondary NMA 5 (bio-IR)
                                     ifelse (nma.number == 8,
                                          nma_data_pre <- final_data %>%
                                           filter(!(Study == 'SELECT_AXIS_2' & Week_outcome_1 == 12)),

                                     print("Number not valid")

                          ))))

 ifelse (nma.endpt == "BASDAICFB",

       nma_data <- nma_data_pre %>%
        filter(!is.na(BASDAI_Chg_1_Mean)) %>%
        mutate(outcome=BASDAI_Chg_1_Mean,
            sampleSize=round(as.numeric(BASDAI_Chg_1_N),0),
            se=BASDAI_Chg_1_SE,
            treatment=Treatment_arm,
            study=Study) %>%
        select(study, treatment, sampleSize, outcome, se),

       ifelse (nma.endpt == "BASFICFB",

            nma_data <- nma_data_pre %>%
             filter(!is.na(BASFI_Chg_1_Mean)) %>%
             mutate(outcome=BASFI_Chg_1_Mean,
```

◊ Clarification questions

```
            sampleSize=round(as.numeric(BASFI_Chg_1_N),0),
            se=BASFI_Chg_1_SE,
            treatment=Treatment_arm,
            study=Study) %>%
          select(study, treatment, sampleSize, outcome, se),

        ifelse (nma.endpt == "TotalBackPainCFB",

            nma_data <- nma_data_pre %>%
             filter(!is.na(TotalBackPain_Chg_1_Mean)) %>%
             mutate(outcome=TotalBackPain_Chg_1_Mean,
                 sampleSize=round(as.numeric(TotalBackPain_Chg_1_N),0),
                 se=TotalBackPain_Chg_1_SE,
                 treatment=Treatment_arm,
                 study=Study) %>%
             select(study, treatment, sampleSize, outcome, se),

            print("Outcome not valid")

        )))

## BNMA data prep ##

bugs_data <- nma_data

bugs_data_global_copy <<- bugs_data


# PBO receives ID=1
bugs_data$treatment[bugs_data$treatment =="PBO"] <- "1PBO"

# Number of treatment arms in each study (na)
bugs_data <- bugs_data %>% group_by(study) %>% mutate(na = n())
max_na <- max(bugs_data$na)

# Order by treatment
bugs_data <- bugs_data[order(bugs_data$treatment),]

# Assign ID to each unique treatment arm (t)
bugs_data$t <- with(bugs_data, ave(as.character(treatment), FUN=function(x)
match(x, unique(x))))
bugs_data$t <- as.integer(bugs_data$t)
bugs_data$treatment[bugs_data$treatment =="1PBO"] <- "PBO"

# Get the mapping of treatment ID and treatment labels

bugs_trt.key <- cbind(bugs_data$treatment, bugs_data$t)
bugs_trt.key <- data.frame(unique(bugs_trt.key, incomparables = FALSE))

colnames(bugs_trt.key) <- c("Treat.order", "Treat_id")
```

- ◊ Clarification questions

```
  assign("Trt.key", bugs_trt.key, envir= .GlobalEnv)

  Treat.order <<- Trt.key$Treat.order

  # The data needs to be order by study
  bugs_data <- bugs_data[order(bugs_data$study, bugs_data$t), ]

  # Assign ID to each study
  bugs_data$Study <- with(bugs_data, ave(as.character(study), FUN=function(x)
match(x, unique(x))))

  study <<-  (bugs_data$study)
  Study <<- as.integer(bugs_data$Study)
  Treat <<- bugs_data$treatment
  nTreat <<- bugs_data$t
  N <<- as.numeric(bugs_data$sampleSize)
  Outcomes <<- bugs_data$outcome #For continuous outcome
  se <<- bugs_data$se #For continuous outcome
  Treat.order <<- bugs_trt.key$Treat.order
  Trt.key <<- bugs_trt.key
  bnma_prepdata <<- list(study, Treat, N, Outcomes, se, Treat.order)

  # Calculate mean and var for PBO
  bugs_data <- reshape2::melt(bugs_data, id.var = c("study", "t"))
  bugs_data <- reshape::cast(bugs_data, study~variable + t)
  mean_pbo <- as.numeric(bugs_data$outcome_1)
  meanA <<- mean(mean_pbo)
  precA <<- 1/(var(mean_pbo))

}
```

NMA Run via BNMA

```
## BNMA model function for continuous outcomes (consistency model) ##

bnma.cont_main <- function(type, baseline_bnma,
                  hy.prior.bl_dist="dunif", hy.prior.bl_a=0, hy.prior.bl_b=5,
                  hy.prior.Eta_dist="dunif", hy.prior.Eta_a=0, hy.prior.Eta_b=5,
                  seed=rsd, RNG.inits=jags_seed) {

  network <- with(bnma_prepdata, network.data(
    Outcomes = Outcomes,
    Study = study,
    Treat = Treat,
    N = N,
    SE = se, #Use only when response=normal
    response = "normal",
    Treat.order = Treat.order,
    type = type,
```

- ◊ Clarification questions

```
  rank.preference = "lower",
  # Covariate adjustment and effect
  covariate = NULL,
  covariate.type = NULL,
  covariate.model = NULL,
  mean.cov = NULL,
  prec.cov = NULL,
  hy.prior.cov = NULL, #For exchangeable only
  # Relative effect
  mean.d = mean.prior,
  prec.d = prec.prior,
  # Study effect (baseline risk)
  baseline.risk = baseline.risk, #Exchangeable, independent
  mean.Eta = mean.prior,
  prec.Eta = prec.prior,
  hy.prior.Eta = list(hy.prior.Eta_dist, hy.prior.Eta_a, hy.prior.Eta_b), #For
exchangeable only
  # Baseline slope
  baseline = baseline_bnma, #Common, exchangeable, independent
  mean.bl = mean.prior,
  prec.bl = prec.prior,
  hy.prior.bl = list(hy.prior.bl_dist, hy.prior.bl_a, hy.prior.bl_b), #For exchangeable
only
  # Prior for the heterogeneity parameter (supports uniform, gamma, and
half normal)
  hy.prior = list(hy.prior_dist, hy.prior_a, hy.prior_b), #dgamma, 0.001, 0.001
  # Standard treatment effect
  mean.A = meanA,
  prec.A = precA))

 set.seed(seed)

 result <- network.run(network,
              inits = NULL,
              n.chains = 3,
              max.run = 1e+05,
              setsize = setsize,
              n.run = run,
              conv.limit = 1.05,
              extra.pars.save = NULL,
              RNG.inits = RNG.inits)

}
```

UME NMA Run via BNMA

```
## BNMA model function for binary outcomes (node split model) ##

bnma.binary_nodesplit <- function(type, pair) {
```

- Clarification questions

```
  network_nodesplit <- with(bnma_prepdata, nodesplit.network.data(
    Outcomes = Outcomes,
    Study = study,
    Treat = Treat,
    N = N,
    SE = NULL, #Use only when response=normal
    response = "binomial",
    Treat.order = Treat.order,
    pair = pair,
    type = type,
    dic = T))

  assign(paste(nma.endpt, nma.number, type, pair, "network", sep="_"),
network_nodesplit, envir= .GlobalEnv)

  result_nodesplit <- nodesplit.network.run(
    network_nodesplit,
    inits = NULL,
    n.chains = 3,
    max.run = 1e+05,
    setsize = setsize,
    n.run = run,
    conv.limit = 1.05,
    extra.pars.save = NULL)
}
```

Selected Model Code for Results Presented in Section B.3.9.2 and associated UME models - bDMARD-naïve

BASDAI CFB - Random Effects (RE)

NMA Run via BNMA Inputs

```
# Specifications
  nma.endpt <- "BASDAICFB"
  nma.number <- 5 #UPA: 14 weeks; Comparators: 12-16 weeks; Mixed bDMARD-
exposure: Excluded
  run <- 100000
  setsize <- 10000
  baseline <- "common"
  baseline.risk <- "independent"
  hy.prior_dist <- "dunif"
  hy.prior_a <- 0
  hy.prior_b <- 5
  mean.prior <- 0
  prec.prior <- .0001

# NMA run
```

- ◊ Clarification questions

```
bnma.binary_main(type="random", baseline_bnma="none")
bnma.binary_ume(type="random")
```

Produced Primary Model Code

```
## model
## {
##  for (i in 1:16) {
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
##  }
##  for (i in 1:16) {
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        tau[i,k] <- 1/pow(se[i,k],2)
##        r[i,k] ~ dnorm(theta[i,k], tau[i,k])
##        theta[i,k] <- Eta[i] + delta[i,k]
##        dev[i,k] <- (r[i,k]-theta[i,k])*(r[i,k]-theta[i,k])*tau[i,k]
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for(k in 2:na[i]){
##        delta[i,k] ~ dnorm(md[i,k],precd[i,k])
##        md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
##        precd[i,k] <- prec *2*(k-1)/k
##        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
##        sw[i,k] <- sum(w[i,1:(k-1)])/(k-1)
##     }
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:12){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  sd ~ dunif(hy.prior.1, hy.prior.2)
##  prec <- pow(sd,-2)
##  logvar <- log(pow(sd, 2))
##  rank_number <- rank(d[])
##  for(k in 1:12){
##     rk[k] <- rank_number[k]
##     for(h in 1:12){ prob[h,k] <- equals(rk[k],h)}
##  }
##  A ~ dnorm(mean.A, prec.A)
##  for(k in 1:12) { T[k] <- A + d[k] }
## }
```

Produced UME Model

```
## model
## {
##  for(i in 1:16) {
##     delta[i,1] <- 0
```

- ◊ Clarification questions

```
##     mu[i] ~ dnorm(mean.mu, prec.mu)
##     for(k in 1:na[i]) {
##        tau[i,k] <- 1/pow(se[i,k],2)
##        r[i,k] ~ dnorm(theta[i,k], tau[i,k])
##        theta[i,k] <- mu[i] + delta[i,k]
##        dev[i,k] <- (r[i,k]-theta[i,k])*(r[i,k]-theta[i,k])*tau[i,k]
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for (k in 2:na[i]) {
##        delta[i,k] ~ dnorm(d[t[i,1],t[i,k]], prec)
##     }
## }
## totresdev <- sum(resdev[])
## for(c in 1:11) {
##     for(k in (c+1):12) {
##        d[c,k] ~ dnorm(mean.d, prec.d)
##     }
## }
## sd ~ dunif(hy.prior.1, hy.prior.2)
## prec <- pow(sd,-2)
## }
```

BASDAI CFB - Random Effects with Baseline-risk Adjustment (REA)

NMA Run via BNMA Inputs

```
# Specifications
 nma.endpt <- "BASDAICFB"
 nma.number <- 5 #UPA: 14 weeks; Comparators: 12-16 weeks; Mixed bDMARD-exposure: Excluded
 run <- 100000
 setsize <- 10000
 baseline <- "common"
 baseline.risk <- "independent"
 hy.prior_dist <- "dunif"
 hy.prior_a <- 0
 hy.prior_b <- 5
 mean.prior <- 0
 prec.prior <- .0001

# NMA run
 bnma.binary_main(type="random", baseline_bnma=baseline)
 bnma.binary_ume(type="random")
```

Produced Primary Model Code

```
## model
## {
##  for (i in 1:16) {
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
```

- ◊ Clarification questions

```
##  }
##  for (i in 1:16) {
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        tau[i,k] <- 1/pow(se[i,k],2)
##        r[i,k] ~ dnorm(theta[i,k], tau[i,k])
##        theta[i,k] <- Eta[i] + delta[i,k]
##        dev[i,k] <- (r[i,k]-theta[i,k])*(r[i,k]-theta[i,k])*tau[i,k]
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for(k in 2:na[i]){
##        delta[i,k] ~ dnorm(md[i,k],precd[i,k])
##        md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] + (b_bl[t[i,k]] - b_bl[t[i,1]]) * (Eta[i] - mx_bl)
##        precd[i,k] <- prec *2*(k-1)/k
##        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) - (b_bl[t[i,k]] - b_bl[t[i,1]]) * (Eta[i] -
mx_bl)
##        sw[i,k] <- sum(w[i,1:(k-1)])/(k-1)
##     }
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:12){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  b_bl[1] <- 0
##  for(k in 2:12){
##     b_bl[k] <- B
##  }
##  B ~ dnorm(mean.bl, prec.bl)
##  sd ~ dunif(hy.prior.1, hy.prior.2)
##  prec <- pow(sd,-2)
##  logvar <- log(pow(sd, 2))
##  rank_number <- rank(d[])
##  for(k in 1:12){
##     rk[k] <- rank_number[k]
##     for(h in 1:12){ prob[h,k] <- equals(rk[k],h)}
##  }
##  A ~ dnorm(mean.A, prec.A)
##  for(k in 1:12) { T[k] <- A + d[k] }
## }
```

Produced UME Model

```
## model
## {
##  for(i in 1:16) {
##     delta[i,1] <- 0
##     mu[i] ~ dnorm(mean.mu, prec.mu)
##     for(k in 1:na[i]) {
```

- ◊ Clarification questions

```
##         tau[i,k] <- 1/pow(se[i,k],2)
##         r[i,k] ~ dnorm(theta[i,k], tau[i,k])
##         theta[i,k] <- mu[i] + delta[i,k]
##         dev[i,k] <- (r[i,k]-theta[i,k])*(r[i,k]-theta[i,k])*tau[i,k]
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for (k in 2:na[i]) {
##         delta[i,k] ~ dnorm(d[t[i,1],t[i,k]], prec)
##     }
## }
## totresdev <- sum(resdev[])
## for(c in 1:11) {
##     for(k in (c+1):12) {
##         d[c,k] ~ dnorm(mean.d, prec.d)
##     }
## }
## sd ~ dunif(hy.prior.1, hy.prior.2)
## prec <- pow(sd,-2)
## }
```

BASFI CFB - Fixed Effects (FE)

NMA Run via BNMA Inputs

```
# Specifications
 nma.endpt <- "BASFICFB"
 nma.number <- 5 #UPA: 14 weeks; Comparators: 12-16 weeks; Mixed bDMARD-exposure: Excluded
 run <- 100000
 setsize <- 10000
 baseline <- "common"
 baseline.risk <- "independent"
 hy.prior_dist <- "dunif"
 hy.prior_a <- 0
 hy.prior_b <- 5
 mean.prior <- 0
 prec.prior <- .0001

# NMA run
 bnma.binary_main(type="fixed", baseline_bnma="none")
 bnma.binary_ume(type="fixed")
```

Produced Primary Model Code

```
## model
## {
## for (i in 1:12) {
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
## }
## for (i in 1:12) {
```

- Clarification questions

```
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        tau[i,k] <- 1/pow(se[i,k],2)
##        r[i,k] ~ dnorm(theta[i,k], tau[i,k])
##        theta[i,k] <- Eta[i] + d[t[i,k]] - d[t[i,1]]
##        dev[i,k] <- (r[i,k]-theta[i,k])*(r[i,k]-theta[i,k])*tau[i,k]
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:9){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  rank_number <- rank(d[])
##  for(k in 1:9){
##     rk[k] <- rank_number[k]
##     for(h in 1:9){ prob[h,k] <- equals(rk[k],h)}
##  }
##  A ~ dnorm(mean.A, prec.A)
##  for(k in 1:9) { T[k] <- A + d[k] }
## }
```

Produced UME Model

```
## model
## {
##  for(i in 1:12) {
##     delta[i,1] <- 0
##     mu[i] ~ dnorm(mean.mu, prec.mu)
##     for(k in 1:na[i]) {
##        tau[i,k] <- 1/pow(se[i,k],2)
##        r[i,k] ~ dnorm(theta[i,k], tau[i,k])
##        theta[i,k] <- mu[i] + delta[i,k]
##        dev[i,k] <- (r[i,k]-theta[i,k])*(r[i,k]-theta[i,k])*tau[i,k]
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for (k in 2:na[i]) {
##        delta[i,k] <- d[t[i,1],t[i,k]]
##     }
##  }
##  totresdev <- sum(resdev[])
##  for(c in 1:8) {
##     for(k in (c+1):9) {
##        d[c,k] ~ dnorm(mean.d, prec.d)
##     }
##  }
## }
```

- Clarification questions

BASFI CFB - Fixed Effects with Baseline-risk Adjustment (FEA)

NMA Run via BNMA Inputs

```
# Specifications
 nma.endpt <- "BASFICFB"
 nma.number <- 5 #UPA: 14 weeks; Comparators: 12-16 weeks; Mixed bDMARD-exposure: Excluded
 run <- 100000
 setsize <- 10000
 baseline <- "common"
 baseline.risk <- "independent"
 hy.prior_dist <- "dunif"
 hy.prior_a <- 0
 hy.prior_b <- 5
 mean.prior <- 0
 prec.prior <- .0001

# NMA run
 bnma.binary_main(type="fixed", baseline_bnma=baseline)
 bnma.binary_ume(type="fixed")
```

Produced Primary Model Code

```
## model
## {
##  for (i in 1:12) {
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
##  }
##  for (i in 1:12) {
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        tau[i,k] <- 1/pow(se[i,k],2)
##        r[i,k] ~ dnorm(theta[i,k], tau[i,k])
##        theta[i,k] <- Eta[i] + d[t[i,k]] - d[t[i,1]] + (b_bl[t[i,k]] - b_bl[t[i,1]]) * (Eta[i] - mx_bl)
##        dev[i,k] <- (r[i,k]-theta[i,k])*(r[i,k]-theta[i,k])*tau[i,k]
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:9){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  b_bl[1] <- 0
##  for(k in 2:9){
##     b_bl[k] <- B
##  }
```

- ◊ Clarification questions

```
##  B ~ dnorm(mean.bl, prec.bl)
##  rank_number <- rank(d[])
##  for(k in 1:9){
##     rk[k] <- rank_number[k]
##     for(h in 1:9){ prob[h,k] <- equals(rk[k],h)}
##  }
##  A ~ dnorm(mean.A, prec.A)
##  for(k in 1:9) { T[k] <- A + d[k] }
## }
```

Produced UME Model

```
## model
## {
##  for(i in 1:12) {
##     delta[i,1] <- 0
##     mu[i] ~ dnorm(mean.mu, prec.mu)
##     for(k in 1:na[i]) {
##        tau[i,k] <- 1/pow(se[i,k],2)
##        r[i,k] ~ dnorm(theta[i,k], tau[i,k])
##        theta[i,k] <- mu[i] + delta[i,k]
##        dev[i,k] <- (r[i,k]-theta[i,k])*(r[i,k]-theta[i,k])*tau[i,k]
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##     for (k in 2:na[i]) {
##        delta[i,k] <- d[t[i,1],t[i,k]]
##     }
##  }
##  totresdev <- sum(resdev[])
##  for(c in 1:8) {
##     for(k in (c+1):9) {
##        d[c,k] ~ dnorm(mean.d, prec.d)
##     }
##  }
## }
```

Selected Model Code for Results Presented in Section B.3.9.2 - bDMARD-IR

BASDAI CFB - Fixed Effects (FE)

NMA Run via BNMA Inputs

```
# Specifications
 nma.endpt <- "BASDAICFB"
 nma.number <- 8 #UPA: 14 weeks; Comparators: 16 weeks; bio-IR
 run <- 100000
 setsize <- 10000
 baseline <- "common"
```

- ◊ Clarification questions

```
baseline.risk <- "independent"
hy.prior_dist <- "dunif"
hy.prior_a <- 0
hy.prior_b <- 5
mean.prior <- 0
prec.prior <- .0001

# NMA run
bnma.binary_main(type="fixed", baseline_bnma="none")
```

Produced Primary Model Code

```
## model
## {
##  for (i in 1:2) {
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
##  }
##  for (i in 1:2) {
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        tau[i,k] <- 1/pow(se[i,k],2)
##        r[i,k] ~ dnorm(theta[i,k], tau[i,k])
##        theta[i,k] <- Eta[i] + d[t[i,k]] - d[t[i,1]]
##        dev[i,k] <- (r[i,k]-theta[i,k])*(r[i,k]-theta[i,k])*tau[i,k]
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:4){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  rank_number <- rank(d[])
##  for(k in 1:4){
##     rk[k] <- rank_number[k]
##     for(h in 1:4){ prob[h,k] <- equals(rk[k],h)}
##  }
##  A ~ dnorm(mean.A, prec.A)
##  for(k in 1:4) { T[k] <- A + d[k] }
## }
```

BASFI CFB - Fixed Effects (FE)

NMA Run via BNMA Inputs

```
# Specifications
 nma.endpt <- "BASFICFB"
 nma.number <- 8 #UPA: 12 weeks; Comparators: 16 weeks; bio-IR
 run <- 100000
```

- ◊ Clarification questions

```
setsize <- 10000
baseline <- "common"
baseline.risk <- "independent"
hy.prior_dist <- "dunif"
hy.prior_a <- 0
hy.prior_b <- 5
mean.prior <- 0
prec.prior <- .0001

# NMA run
bnma.binary_main(type="fixed", baseline_bnma="none")
```

Produced Primary Model Code

```
## model
## {
##  for (i in 1:2) {
##     Eta[i] ~ dnorm(mean.Eta, prec.Eta)
##  }
##  for (i in 1:2) {
##     w[i,1] <- 0
##     delta[i,1] <- 0
##     for(k in 1:na[i]){
##        tau[i,k] <- 1/pow(se[i,k],2)
##        r[i,k] ~ dnorm(theta[i,k], tau[i,k])
##        theta[i,k] <- Eta[i] + d[t[i,k]] - d[t[i,1]]
##        dev[i,k] <- (r[i,k]-theta[i,k])*(r[i,k]-theta[i,k])*tau[i,k]
##     }
##     resdev[i] <- sum(dev[i,1:na[i]])
##  }
##  totresdev <- sum(resdev[])
##  d[1] <- 0
##  for(k in 2:4){
##     d[k] ~ dnorm(mean.d,prec.d)
##  }
##  rank_number <- rank(d[])
##  for(k in 1:4){
##     rk[k] <- rank_number[k]
##     for(h in 1:4){ prob[h,k] <- equals(rk[k],h)}
##  }
##  A ~ dnorm(mean.A, prec.A)
##  for(k in 1:4) { T[k] <- A + d[k] }
## }
```

- ◊ Clarification questions

NICE National Institute for Health and Care Excellence

Patient organisation submission

Upadacitinib for treating active ankylosing spondylitis ID3848

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

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

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

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

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

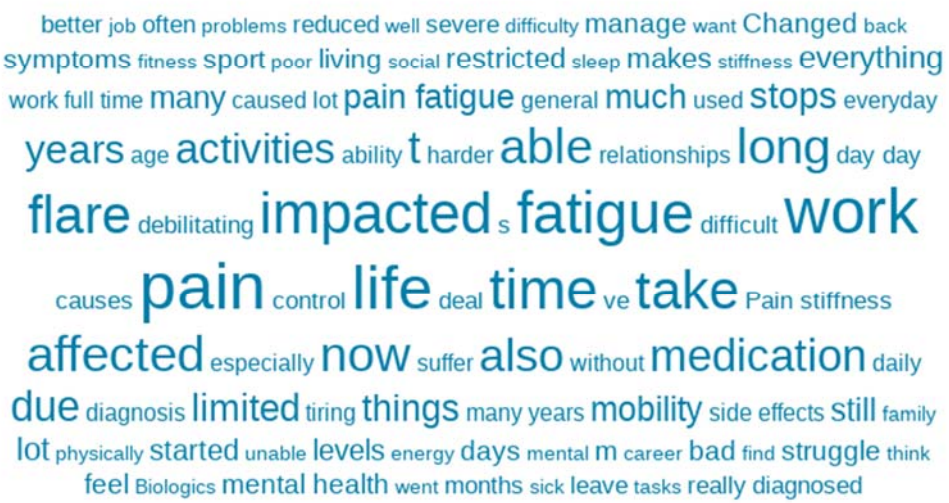
About you	
1.Your name	[redacted]

2. Name of organisation	National Axial Spondyloarthritis Society
3. Job title or position	[redacted]
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 4,035 members, the majority of which have axial SpA (AS).
4b. 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.	

Abbvie Ltd	Aspiring to Excellence Quality Improvement programme	30,000.00
UCB	All Party Parliamentary Group secretariat	16,000.00
UCB	Act on Axial SpA: A Gold Standard Time to Diagnosis	287,681.00
Biogen	Aspiring to Excellence Quality Improvement programme	30,000.00
Novartis Investment	All Party Parliamentary Group secretariat	16,000.00
Novartis Investment	Round table policy meeting in axial SpA	11,900.00
Novartis Investment	Aspiring to Excellence Quality Improvement programme	30,000.00
E. Lilly	Aspiring to Excellence Quality Improvement programme	30,000.00

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We carried out a snapshot survey of our members and followers from 4 December to 10 December 2021, to which we received 192 eligible responses. The questions were based on those included in the submission template, and were a mix of closed and open ended questions. We were able to gather from a good demographic, with 38% of respondents under 45 and with 37% being diagnosed less than 5 years ago. In terms of ethnicity, the group were largely white (95%), with 58% considering themselves to be disabled.
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."*

	Q8 Why do you say that? 
Current treatment of the condition in the NHS	
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. Whilst the corner stones of treatment are anti inflammatory medication and exercise, there are those (XX%) 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 ankylosing spondylitis to be able to exercise more easily and to live a fuller life.
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 accomodation
Other issues	
13. Are there any other issues that you would like the committee to consider?	There was an overall positive response to the new drug and its possibilities.
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.

Thank you for your time.

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

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Upadacitinib for treating active ankylosing spondylitis ID3848

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 (SIG)**
2. Name of organisation	**British Society for Rheumatology (BSR)**

3. Job title or position	
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**British Society for Rheumatology (BSR)**
4b. 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.	
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	Reduction in BASDAI and spinal pain VAS by 2 points

x cm, or a reduction in disease activity by a certain amount.)	
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 AS
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
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance on management of spondyloarthritis
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Pathway of care is generally well-defined but there may be local variability depending on local expertise, resources and agreement re funding of targeted therapies

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Provide additional option 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
• How does healthcare resource use differ between the technology and current care?	This is a first oral small molecule agent in the treatment of ankylosing spondylitis.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	n/a

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
• Do you expect the technology to increase length of life more than current care?	no
• 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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	May be easier for some patients, being orally administered rather than s/c
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 patient is eligible to start and continue treatment, used in 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
• Is the technology a 'step-change' in the management of the condition?	Yes – drug with new mechanism of action
• Does the use of the technology address any particular unmet need of the patient population?	There is 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 AS, 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 a new medication with potential side effects.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• 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.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No new safety risks identified that we are aware of
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 treatments since the publication of NICE technology appraisal guidance TA383, TA407, TA497, TA718 and TA719?	Phase 3 trial published 2021
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 AS, 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 AS • 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

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Upadacitinib for treating active ankylosing spondylitis [ID3848]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your 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. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Friday 20 May 2022.**

Completing this form

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with this condition and current treatment options	
About you	
1. Your name	**Dr Raj Sengupta**
2. Name of organisation	**Royal National Hospital for Rheumatic Diseases, Bath**
3. Job title or position	**Consultant Rheumatologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it

encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Upadacitinib is a selective JAK-1 inhibitor with a large clinical trial programme demonstrating clinical efficacy in axial spondyloarthritis (including non radiographic and radiographic axial spondyloarthritis), rheumatoid arthritis and psoriatic arthritis. The main aim of this treatment in axial spondyloarthritis (axSpA) is to improve patients quality of life by reducing pain and stiffness, improving sleep and fatigue levels. This leads to reduction in disability with the improving of physical function and spinal mobility. Inhibition of radiographic progression using the mSASSS score has been demonstrated with Upadacitinib in the clinical trials.

9. 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.)	A clinically significant treatment response would be a reduction of the BASDAI by either 50% or 2 points and the reduction of the spinal pain score by 2 points.
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There continues to be an unmet need in axSpA patients due to limited treatment choices – at present, there are 2 modes of action. Studies have shown approximately 50% of patients achieving an ASAS40 response with their first biologic. Patients stop their drugs due to inefficacy (primary and secondary) or side effects. Additionally, unmet needs for this group of patients include suboptimal pain control and the achievement of remission. The current modes of action with anti TNFs and anti IL17 can be associated with disease related side effects as well as not being suited to patients with certain extra musculoskeletal manifestations of the disease - eg inflammatory bowel disease. Therefore an alternative mode of action will be helpful in ensuring these patients are treated appropriately. Furthermore, axSpA patients are young and maybe keener to have an oral therapy rather than injections which some patients deem to be associated with severe, progressive disease. There will also be a population of axSpA patients with needle phobia and it would be an asset to our treatment paradigm to have an oral formulation eg convenience of an oral preparation and easy storage, travelling.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Physiotherapy and anti inflammatories are the initial treatments used for patients with axSpA. When symptoms are not controlled with the above, patients are considered for biologic and targeted synthetic disease modifying drugs (b/tsDMARDs) if they meet NICE criteria.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines (NG65, TA383, TA407 and TA718) and BSR guidelines
• 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.)	The pathway of care in axSpA is well defined. Initiation and response criteria are well established and used by all health care professionals in the UK
• What impact would the technology have on the current pathway of care?	This technology is an important addition to the treatment options currently available for axSpA patients. For patients who have a lack of response or side effects to currently available therapies, this technology will provide a further option for treatment. In addition, the once daily oral formulation does also provide an alternative and will be welcome by some patients. This technology has a different mode of action to currently available therapies providing a further treatment option for axSpA patients
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used within current practice guidelines for treating patients with axial spondyloarthritis. In my opinion, this technology should be made available for use as a choice of treatment after the use of biosimilars. This is in keeping with NICE guidance stating that the most cost effective treatment should be used where appropriate. The technology should therefore be made available **along side** non biosimilar TNF blockers and IL17 treatments. axSpA patients with high disease activity (BASDAI and back pain score>4) will be eligible for this technology. This will be in line with current bDMARD prescribing in the UK.
• How does healthcare resource use differ between the technology and current care?	This technology provides an alternative mode of action as there are only TNF blockers and IL17 blocker treatments currently available. This would have no impact on current healthcare resource.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In keeping with other DMARDs, this technology should only be prescribed by secondary care rheumatologists
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. I do expect the technology to provide clinical meaningful benefits comparable to existing treatment choices available (anti TNF and anti IL17 therapies).
• Do you expect the technology to increase length of life more than current care?	N/A
• Do you expect the technology to increase health-related quality of life more than current care?	One of the strengths of this technology, in my opinion, is the significant positive effect this technology has on patients quality of life. The data from the clinical trials supports this statement and suggests that the benefits are comparable to currently available biologics.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology should be considered in axSpA patients who have had non response, loss of response or side effects from biosilimilar TNF blockers. It should also be made available to axSpA patients who are not suitable for anti TNF therapy 1st line. I would expect this technology to be effective in all axSpA patients with varying clinical manifestations.
The use of the technology	
15. 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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This technology should be easier for patients to use as no training for injections are required. Benefits comparable to currently available biologics can be achieved with this oral tablet formulation. There are no concomitant treatments required. Baseline screening are similar to those required for patients starting other formulations except for the addition of baseline lipid testing
16. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Current NICE treatment guidelines for axSpA will be used for initiating and stopping this technology. The patients' BASDAI would have to improve by 50% or 2 points and the back pain score by 2 points when assessed at week 12 after starting the treatment.

Do these include any additional testing?	No additional testing required.
17. 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?	No
18. 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?	This technology is innovative for 2 main reasons – it is a different mode of action to the currently available treatments. In addition, it's the 1st once daily oral agent available for treatment for axSpA with efficacy that's comparable to TNF blockers and anti IL17 therapy.
• Is the technology a 'step-change' in the management of the condition?	This technology is a step change in the management of axSpA patients for the reasons outlined above.
• Does the use of the technology address any particular unmet need of the patient population?	The biggest unmet need in axSpA currently with available therapies is adequate control of pain and achievement of remission. Patients with needle phobia would also be suitable for this treatment. In addition, for patients with interstitial lung disease, multiple sclerosis or family history of multiple sclerosis who are unable to have anti TNF

	would be suitable for this treatment. Finally, patients with active inflammatory bowel disease who would not be suitable for anti IL17 therapy, could be treated with this technology
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The clinical trials programme for this technology have not highlighted any significant adverse events in line with data from anti TNF and anti IL17 clinical trials. Whilst caution should be exercised when considering prescribing JAK inhibitors for patients with high baseline risk for thromboembolic disease, it is important to note that for axSpA patients treated with this technology, no VTEs were seen in the clinical trial. For other adverse events, we would stop the technology and switch the patient to an alternative therapy as we would with all currently available advanced therapies.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the clinical trial for this technology in axSpA patients does closely reflect current UK clinical practice. The inclusion and exclusion criteria of studies are reflective of clinical practice as are the baseline characteristics
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important clinical outcomes measured in this study are BASDAI and spinal pain scores – outcomes used in routine clinical practice in the UK. In addition, objective markers of disease activity and damage were also measured (CRP, MRI and xrays)
• If surrogate outcome measures were used, do	N/A

they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA407 and TA718?	No
23. How do data on real-world experience compare with the trial data?	There isn't any significant real world data published with this technology
Equality	

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
25. If recommended, how likely is upadacitinib to be used instead of secukinumab or ixekizumab for treatment of AS?	Upadacitinib should be available 2nd line after biosimilar anti TNF. In my opinion, it will probably used in similar proportions to Secukinumab and Ixekizumab. The prescribing of the appropriate 2nd line drug (either IL17 inhibition or Upadacitinib) should be made by the clinician and patient.
27. Would you expect any differences in adherence to upadacitinib compared to secukinumab or ixekizumab due to its oral administration?	I would not expect any significant differences in adherence to upadacitinib when compared to anti IL 17 therapy. Firstly, the clinical trials showed good patient adherence to treatment throughout the trial with compliance in the SELECT-AXIS studies being over 97%. Secondly, it is my experience that when a drug is effective, it is always taken by the patient regularly – patients in the SELCT-AXIS study showed that clinical benefit was sustained through to week 64. Thirdly, we can never fully control how adherent patients are to every drug we prescribe, including TNF blockers and anti IL17 therapy – anecdotally, patients have informed me of situations where they have delayed

	administering injections. Finally, an oral once a day preparation is unlikely to be a problem for patients where adherence is concerned.
28. Would you expect upadacitinib to have a different adverse event profile to secukinumab or ixekizumab in the population it will be used in?	I would not expect to see a different adverse effect profile with these drugs. Studies with Upadacitinib have not highlighted any significant differences when compared to biologic DMARDs. There is now 4 and half year safety data with Upadacitinib. In addition, the clinical trial with Upadacitinib had a Adalimumab comparator arm and the study did not highlight any safety concerns with Updadacitinib. I do believe that clinicians are careful when selecting DMARDs for patients with axSpA and the careful risk profiling of patients prior to starting these agents ensures minimal adverse events being seen in clinical practice. Finally, the shorter half life of Upadacitinib should be taken into account – if the patient was to have an adverse event, the patient is likely to improve quicker from the adverse event when Upadacitinib is stopped compared to the anti IL17 therapies which are administered monthly.
29. Would you expect upadacitinib to have different discontinuation rates over time to secukinumab or ixekizumab?	I would not expect different discontinuation rates between these agents over time. This is demonstrated in the clinical trials where discontinuation rates were low. Whilst there are no head to head studies, the comparable clinical benefit and adverse event profile with Upadacitinib and IL17 blockers would suggest that we are likely to see similar discontinuation rates in clinical practice.
30. Would you expect upadacitinib to maintain the efficacy seen in the SELECT-	I would expect the efficacy seen in the SELECT-AXIS studies to be maintained in the longer term. The benefit of Upadacitinib over 64 weeks is evident in the SELECT-AXIS studies and is very comparable to previous anti TNF and anti IL17 studies. Therefore, there is no reason to believe that the longer term efficacy is going to be any different in the real world when Upadacitinib is used.

AXIS1 and SELECT-AXIS2 trials in the longer term?	

PART 2 -Key messages
31. In up to 5 sentences, please summarise the key messages of your statement: • Upadacitinib should be made available as a treatment option in axSpA alongside anti TNF and IL17 blockers • Upadacitinib provides a new mode of action as well as a novel mode of administration for the treatment of axSpA patients. • Upadacitinib should be prescribed in line with current axSpA treatment guidelines • Adherence to Upadacitinib in clinical trials is comparable to bDMARDs • Upadacitinib has a good safety profile in the SELECT-AXIS studies

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Upadacitinib for treating active ankylosing spondylitis [ID3848]

Thank you for agreeing to give us your views on this treatment 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.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.
In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Thursday 19 May 2022**

Completing this form
Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you want 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 15 pages.

PART 1 – Living with or caring for a patient with this condition and current treatment options	
About you	
1.Your name	**Frances Reid**
2. Are you (please tick all that apply):	**X** a patient with this condition? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? X a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	National Axial Spondyloarthritis Society
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission

	☐ I agree with it and **do not wish to** complete this statement X ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	**X** I am drawing from personal experience. **X** I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: Discussion with members of my local NASS branch (Cambridge) ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference **x** I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference. The teleconference was held on the same day and time as the deadline! ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with this condition? If you are a carer (for someone with this condition) please share your experience of caring for them.	I live with Axial Spondyloarthritis. 3 years ago it was classified as non-radiographic, but was diagnosed via clinical history and MRI. Since I've not had scans or xrays since, it is not possible to say if I have progressed to Ankylosing Spondylitis. I chair the Cambridge Branch of NASS, and regularly talk with others who have both Ankylosing Spondylitis, and Non-Radiographic Axial Spondyloarthritis. Every day my life is affected by my condition, both physically and mentally. In the years leading up to diagnosis I had spells where my condition was quiet, and others where it was more active, but in that time I required an early hip replacement due to damage caused by inflammatory arthritis.

	Since my diagnosis, I have been on a rollercoaster, trying to find the best combination of treatments that I can not only tolerate, but which impact sufficiently on my condition. It has taken 3 years to be in a better place, and no one is sure how long that will last, and I still vary from day to day. Frequent night time waking due to pain and stiffness has one of the biggest impacts on my mood, energy, and ability to cope. A good night at the moment is still getting up 2 or 3 times. A reasonable night in my book would be 4 or 5 times. A bad night might be 10+ times a night. More than two or three of those in succession have a hugely detrimental impact on my ability to work and function. To put it into context, until my most recent treatment regime, I would have maybe 1 good night a month. I left my full time job in London some 6 years ago as I was struggling with pain, and overload on top of commuting and looking after my children. I was diagnosed with anxiety and depression, but taking a year out, medication to help, a lot of exercise and physio, and CBT all helped. I am lucky now to work as a freelancer, from home, mainly working for a global health organisation where I can vary my hours to manage fatigue and pain. I work on average 3 days a week, but spread out over 5 days. Every day I have to be careful what I eat and drink, and what I do for exercise (walking, stretching, hydrotherapy, specialist exercise classes, but not too much of any one activity). Doing the wrong thing triggers flares. I can no longer go to a supermarket to do a big shop, or clean my own home, and I have to juggle what activities I need to do with what I want to do, so that I can manage. I cannot sit for long without becoming very stiff. I also attend a private physio once a month. I can have pain almost anywhere, but of particular issue are my SI joints, neck, and enthesitis in hands, and feet – I have had Plantar Fasciitis and Achilles Tendinitis for over 2 years. I can no longer perform as a singer (I was trained as one) due to the challenges of standing as a soloist or in a choir for performances). I also have to deal with psoriasis flares on my hands and feet. For a period of around 2 years I was very prone to falls (about 5 or 6 a year), on one occasion resulting in

	significant facial/dental injury), and on another, cracked ribs. So the impact of the disease is very significant. In terms of my treatment history I have tried the following drugs: I hope it highlights the challenging journey of trying to find the best treatment regime, that is common for many - Ibuprofen (pre-diagnosis, in relation to a knee injury that did not heal for 6 months, but this gave me chemical gastritis) - Naproxen (on diagnosis) however this did not help sufficiently (3 months) - Meloxicam (after the Naproxen). This worked better but was not sufficient to control the pain (approx. 2 years) - Adulimumab. I spent a year on this drug, even though it really was not helping much at all, and caused significant side effects, including frequent infections, and in the early days overwhelming fatigue which contributed to my major fall. However, due to Rheumatology appointment timings, and the start of the pandemic, I was not switched to a new drug until 12 months after I started it. I was on Meloxicam during this time - Secukinumab. The best response I have ever had to drug treatment was on this drug, together with Meloxicam during the loading dose stage. I was a completely different person. However the monthly dose of 150mg was not sufficient. That was increased to 300mg. At this point I developed a gut reaction that was gastritis once again and I had to stop Meloxicam. This led to a deterioration. - Celecoxib. Six months without NSAIDS was detrimental to my condition, even whilst on Secukinumab, so Rheumatology agreed to try Celecoxib as well, however despite all the stomach protectors my gastritis returned quickly. - Methotrexate. I am now on methotrexate with Secukinumab and after 3 months feel good progress is being made, though as yet my liver function

	has not quite settled down. I am more flexible, sleep better, have more energy (generally). Still prone to some stiffness and pain, but quite different from before. - I will be reviewed in a couple of months to determine whether or not the Secukinumab is working well enough and whether or not I need to change biologic again
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	There are a number of medical treatments available. Whilst there currently is guidance on what to try first (NSAIDs, then Adulimumab) it can take a while to get through these if they are not effective, during which time people can experience significant disease progression. Overall, I think the more options there are the better, as finding the treatment that works for any particular patient (or combination of treatments) takes time and is affected by so many factors. I do have a concern that in some areas only three biologics can be used. If a treatment is licensed and approved by NICE then it should not be rationed by local areas. All the current biologics are injections, which once people get used to them are ok, but the option to have a tablet form may be welcomed particularly by those who are needle-phobic, or who find the fridge storage of the injections tricky, for example if travelling, or in shared accommodation. In talking with others, I hear a similar story of trial and error in finding the right drug, and the need for hope that something will work. This is why it is important to have different drug mechanisms as options (anti TNF, IL17A and 23 inhibitors, and now hopefully JAK inhibitors). There is a lot of initial fear over injections and side effects or risks, but those usually dissipate once therapy has started if it is effective.
8. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how	Disadvantages of current treatments are that the biologics are injectable. For some this is a scary prospect and actively puts them off trying them, in addition to fear over side effects. However, for those who get good relief from their biologics, you will hear people describe it as ‘transformational’, and life-changing.

the treatment is given or taken, side effects of treatment etc) please describe these	Storage can be an issue – having to refrigerate injections means that around holiday times or trips for work, it can be hard to arrange safe transportation, or patients have to miss doses with negative effects. It may also be an issue for people in shared accommodation, where they cannot rely on others to make sure the injections are stored in the optimum conditions, and who do not wish to have overt signs of their medical condition on display to others. Some of the current treatments may have particular side effect profiles that make them unusable for some patients. Secukinumab was selected for me, not just because I failed my adalimumab, but we discussed the benefits of prevention of uveitis, and the risk of bowel issues. I am blind in one eye, and do all I can to prevent damage to my good eye. Whilst I have not had uveitis, my mother had repeated bouts of it, so I am aware I may be prone, given her side of the family has a strong history of inflammatory arthritis/psoriasis. Being immunosuppressed is a big issue for patients, but from my experience the level to which I'm prone to infection seems to have lowered since I changed biologic. Having a choice of treatments, may mean that people can find one that suits them better.
Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	The advantages of the proposed treatment are that because it involves a new mechanism of action it may benefit others who have previously not been able to find any relief. The fact that it is an oral tablet taken daily may mean it is easier for patients to comply, and the storage issue is also an important factor. It does not require special conditions. Brain fog can be a significant issue, so trying to remember when your injection is due can be an issue. Although it is easy to say I take it on the '15th of the month' for example, that schedule invariably gets disrupted if there are infections, surgeries, etc.

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	9b. For me the most important factor is the increased choice of treatments. My experience has shown me that side effects or pre-existing conditions may well limit choice if one particular treatment is not effective or stops working. 9c. This new treatment would overcome the issues of storage and having to self-inject.
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	If I were offered this treatment I would seriously consider it, if it might work better than my current combination, but I would want to have a serious discussion about the risks of clots which are flagged in the side effects. It is also not suitable for people over the age of 65. Whilst most AS patients are younger, there are a significant number of us who are older, either diagnosed late, or who have been struggling on treatments for years. If I went onto it at the age of 58, would I have to come off at the age of 65? If it were working well, that would be an incredibly hard thing to do. The only disadvantage I can think of applies to the current ones as well. There is no way of knowing a patient's likely reaction to treatment. The sooner some sort of biomarker can be developed to determine the BEST option for an individual patient the better, as a lot of time can pass before effective solutions are found, and in that time patients are increasingly disabled and at risk of exclusion from work and social activities.

Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Students or others who live in shared accommodation may benefit – having to share fridges with others, and have such an obvious statement of 'ill-health' visible to others can be quite stigmatising, so a tablet form would be welcomed. This would also apply to those who are needle-phobic or find the physical act of self-injecting difficult. It may also be more appealing to people who care about the amount of waste that injections/packaging/sharps bins Older people (over 65s) may miss out, and those who may also be at risk of clots. This might be pertinent for people who have had COVID recently.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race,	The danger in not allowing this treatment is that some people who do not respond well to other treatments or can no longer take them due to waning efficacy or side effects are left without options, rendering them with an increased chance of outcomes such as disability/chronic pain/ inability to work or socialise, thus marginalising them even further. Providing this treatment may prevent people deteriorating to the point that they become disabled (registered or otherwise).

religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 3 -Key messages

14. In up to 5 sentences, please summarise the key messages of your statement:

- It is important to have a range of treatments, and new mechanisms of action to treat this disease, as for most people there is not a simple 'treatment journey'
- Being able to choose an oral medication that does not need special storage, rather than one that is self-injected and has to be stored in a fridge is important.
- Treatment for Axial Spondyloarthritis/Ankylosing Spondylitis often entails trialling different drugs, and different combinations of drugs to find what works best for an individual patient. It would be easier if tests could determine what will work best, but until then it is trial and error. That takes time and have a detrimental effect on mobility/ability to function and mental health.
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Upadacitinib for treating active ankylosing spondylitis [ID3848]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with this condition and current treatment options	
About you	
1.Your name	**Thomas Prior**
2. Are you (please tick all that apply):	**X**☐ a patient with this condition? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	NASS
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) X☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐X Yes, I authored / was a contributor to my nominating organisations submission

	☐ I agree with it and **do not wish to** complete this statement X☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ **X** I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with this condition? If you are a carer (for someone with this condition) please share your experience of caring for them.	I have endured 30 years of living with AS and my home life, work life & sex life has suffered from this complex and challenging disease. I am in almost constant pain particularly in my sacroiliac joints, lumber spine, hips and pelvis. Regular 'flares' of my condition is also a feature of this disease as is chronic fatigue. I have persistent raised inflammatory markers. Working with the condition was very difficult as the disease is not well known, and employers were somewhat sceptical when "flare-ups" happen, and fatigue takes its toll. I had numerous attacks of uveitis but would still have to work on a computer despite having blurred vision and administering steroid eye drops, sometimes every half hour.

	I finally became self-employed but towards the end of my career fatigue and inflammation became increasingly a problem despite being on anti-TNF medication. I had to reduce my hours drastically and apply for Personal Independence Payments (PIP). On the PIP assessment I scored no points at all, but this was overturned at a tribunal and was awarded payments. As my spine is fused, this has impacted on my ability to perform self-care and my wife has to help me dress the lower-half of my body. With two active daughters I could not participate in playing games as much as I wanted or liked when they were growing up. The most heart-breaking for me at the moment is when my toddler grandson stretches out his arms to be picked up and I am unable to bend down to do so.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I am led to believe that all treatments are immunosuppressant, and all have associated health risks. I believe I was one of the first people to trial Etanercept but that was stopped due to adverse effects. I was then given Humira but this too was changed for Amgevita which was stopped due to infected hip replacement. I know of other people who have benefitted from ant-tnf therapy.
8. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how	Having to inject oneself fortnightly is a big disadvantage. Also having to travel abroad with biologic medicine makes it a difficult proposition. I am aware that this medicine also suppresses the immune system. There is an increased risk of recurrent shingles infection.

the treatment is given or taken, side effects of treatment etc) please describe these	Impairment of renal functions
Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	I believe one advantage is that this treatment can be taken in tablet form.
9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	I am unable to speculate on the advantages of this treatment over current treatments.
9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	Yes, in the fact that it can be taken orally and can be taken abroad much easier.
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe	I understand there is the risk of increased shingles infections. However, my rheumatologist has pre-empted this and contacted my GP to arrange for me to have a shingles vaccination.

these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	As I had an infection in my left hip replacement in 2019 whilst taking Amgevita I have it in the back of my mind as to whether this medicine allowed the infection to take hold due to my immune system being suppressed. I am concerned that upadacitinib will affect my immune system and may increase the risk of infection if prescribed to me. However, I believe the benefits will outweigh these concerns.
Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Unable to comment on this point.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any	None that I am aware of.

groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	No.

NICE National Institute for Health and Care Excellence

PART 3 -Key messages
14. In up to 5 sentences, please summarise the key messages of your statement: • Having tried other medicines due to inefficacy and adverse effects I feel that having updacitinib prescribed to me, hopefully in the near future, is the light at the end of a dark tunnel in managing my symptoms and improving my quality of life. • The ability to take this medicine orally would be a vast improvement over injections.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Evidence Review Group's Report

Fast Track Appraisal – cost comparison

Upadacitinib for treating active ankylosing spondylitis [ID3848]

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Ruth Walker, Research Fellow, CRD, University of York Mark Corbett, Research Fellow, CRD, University of York Lucy Beresford, Research Fellow, CRD, University of York Sumayya Anwer, Research Fellow, CRD, University of York Ana Duarte, Research Fellow, CHE, University of York Helen Fulbright, Information Specialist/Research Fellow, CRD, University of York Han Phung, Research Fellow, CHE, University of York Marta Soares, Senior Research Fellow, CHE, University of York Claire Rothery, Senior Research Fellow, CHE, University of York Matthew Walton, Research Fellow, CRD, University of York Sofia Dias, Professor, CRD, University of York
Correspondence to	Professor Sofia Dias, CRD, University of York, York, YO10 5DD
Date completed	16/02/2022

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135430.

Declared competing interests of the authors

None.

Acknowledgements

We would like to thank Dr Deepak Jadon (Addenbrooke's Hospital, Cambridge) and Dr Ram Laxminarayan (University Hospitals of Derby and Burton) for their valuable clinical advice throughout the project. Dr Jadon reports honoraria from AbbVie in the last 12 months for participating in advisory boards for upadacitinib for different disease areas. Dr Jadon is also co-director of an education company (Spondyloarthritis Training and Education SPATE (UK) Ltd.)

which hosts medical education meetings for doctors, nurses and physios with pharma sponsors (including AbbVie). However, Sponsors do not contribute to the selection of faculty, programs, talk content or slide review and their products are not promoted during the talks or education sessions. More information is available at https://rheumatologyevents.org.

We are grateful to Connor Evans for proof-reading a draft version of this report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Walker R, Corbett M, Beresford L, Anwer S, Duarte A, Fulbright H, Phung H, Soares M, Rothery C, Walton M, Dias S. Upadacitinib for treating active ankylosing spondylitis: A Fast Track Appraisal. CRD and CHE Technology Assessment Group, University of York, 2022.

Contributions of authors

Ruth Walker wrote the critique of the systematic review and clinical effectiveness evidence. Mark Corbett wrote the critique of the decision problem and safety evidence. Lucy Beresford and Sumayya Anwer contributed to the critique of the network meta-analyses. Helen Fulbright wrote the critique of the search strategies. Ana Duarte contributed to the critique of the economic evidence. Han Phung contributed to model validation. Matthew Walton contributed to the critique of the economic evidence, conducted the economic analyses, and took overall responsibility for the economics section. Marta Soares provided leadership support to the economic section early in the project and reviewed the final report. Claire Rothery contributed to the critique of the economic evidence, provided leadership support and reviewed the final report. Sofia Dias was project lead, supported the critical appraisal of the evidence and takes responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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List of abbreviations

AE	Adverse event
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASASPR	Assessment of ankylosing spondylitis – partial remission
ASDAS	Ankylosing Spondylitis Disease Activity Score
axSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
bDMARD	Biologic DMARD
BMI	Body mass index
BNF	British National Formulary
CFB	Change from baseline
CI	Confidence interval
CrI	Credible interval
CRP	C-reactive protein
CS	Company submission
csDMARD	Conventional synthetic DMARD
CSR	Clinical study report
DIC	Deviance information criterion
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
DSU	Decision Support Unit
EPAR	European public assessment report
ERG	Evidence review group
FDA	Food and Drug Administration
FE	Fixed effect
FTA	Fast track appraisal
HCHS	Hospital & community health services
HLA-B27	Human leukocyte antigen B-27
HRQoL	Health-related quality of life
HTA	Health technology appraisal
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IGRA	Interferon gamma release assay
IL-17A	Interleukin-17A
JAK	Janus kinase
MACE	Major adverse cardiovascular events
MD	Mean difference
MHRA	Medicines and Healthcare products Regulatory Agency
MTA	Multiple technology appraisal
NHS	National Health Service
NHSCII	NHS cost inflation index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient access scheme
PASI	Psoriasis Area and Severity Index

PSSRU	Personal Social Services Research Unit
Q4W	Every 4 weeks
QFT-GIT	QuantiFERON-TB Gold-In Tub
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RE	Random effect
SAE	Serious adverse event
SC	Subcutaneous
SmPC	Summary of product characteristics
TA	Technology appraisal
TB	Tuberculosis
TNF	Tumour necrosis factor
TSD	Technical Support Document
UK	United Kingdom
VTE	Venous thromboembolism

EVIDENCE REVIEW GROUP REPORT: FAST TRACK APPRAISAL (FTA)

1 SUMMARY OF THE ERG'S VIEW OF THE COMPANY'S FTA CASE

1.1 Safety of upadacitinib

The summary of product characteristics (SmPC) for upadacitinib advises it to be used with caution in patients at high risk of venous thromboembolism (VTE); estimates suggest around a quarter of ankylosing spondylitis (AS) patients have obesity as a risk factor. Considering that other patients may develop VTE risk factors whilst taking upadacitinib, it is evident that a cautious approach is needed when deciding to prescribe upadacitinib. The evidence review group (ERG) notes that upadacitinib, filgotinib, baricitinib and tofacitinib (all Janus kinase (JAK) inhibitors) all have the aforementioned SmPC special warnings and precautions on use in patients with risk factors for deep venous thrombosis and pulmonary embolism. The ERG's clinical advisers also alerted the ERG to Medicines and Healthcare products Regulatory Agency (MHRA) safety warnings on tofacitinib in patients with cardiovascular, malignancy or other specific risk factors. It is currently not known whether other JAK inhibitors would also be affected by this broader group of serious safety outcomes.

There are grounds to doubt the claim for similarity of safety outcomes of upadacitinib when compared with biologic disease modifying anti-rheumatic drugs (bDMARDs), given the extent to which the upadacitinib SmPC advice on cautionary use affects the AS population, and the uncertainty about the extension of concerns about cardiovascular and malignancy events to all JAK inhibitors.

1.2 Pathway position and comparators

The company stated that the most relevant comparators for upadacitinib would be Interleukin-17A (IL-17A) inhibitors (secukinumab and ixekizumab) in either the bDMARD-naïve or -experienced populations. The ERG's clinical advisers considered secukinumab to have a very small market share (around 5%) as a first-line (i.e. bDMARD-naïve) therapy and ixekizumab an even smaller share. No clear clinical rationale was provided by the company for not using a tumour necrosis factor-alpha (TNF-alpha) inhibitor as a first-line comparator. The ERG considers the first-line comparator choices to be sub-optimal in terms of market share and representativeness of therapies used in practice. Given the aforementioned safety concerns, and clinical advice to the ERG, it is highly plausible that for most AS patients (though not all), upadacitinib may be used as a new line of therapy or it may sometimes displace the use of a second IL-17A inhibitor or, very rarely, be used as a first-line treatment in needle-phobic patients.

If used as a new line of therapy (i.e. the last line of therapy), then the relevant comparator would be established clinical management without bDMARDs, which was not mentioned in the National Institute for Health and Care Excellence (NICE) scope. This would not be a suitable comparator for the fast track appraisal (FTA) process as it would not adequately represent NICE recommended treatments as a whole in terms of cost and effects.

1.3 Similar effectiveness relative to selected comparators

The ERG considers non-inferiority of upadacitinib relative to the selected comparators to be plausible on the basis of the evidence presented, albeit caveated by a number of uncertainties. The company submissions (CS) presented network meta-analyses (NMAs) that showed no evidence of differences between upadacitinib compared to secukinumab and ixekizumab in bDMARD-naïve and -experienced patients. However, these analyses were limited by the small number of studies included in the bDMARD-experienced networks.

1.4 Similarity of costs across interventions

For comparison of treatment acquisition costs, inclusive of patient access scheme (PAS) discounts for upadacitinib, secukinumab, and ixekizumab, please refer to the confidential appendix. Costs relating to monitoring may have been underestimated for upadacitinib, and costs relating to the treatment of adverse events (AEs) were not included. The magnitude of these costs and their relevance to upadacitinib and the comparators represents a source of uncertainty. The robustness of the results of the cost comparison analyses is further affected by the areas of uncertainty highlighted below (Sections 1.5, 1.6, 1.7 and 1.8). The ERG also notes that the appropriateness of assessing the cost-effectiveness of upadacitinib in the context of a cost comparison FTA relies on the validity of the assumption of equivalent efficacy and safety (adherence and discontinuation) to at least one relevant comparator.

1.5 Long-term efficacy: area of uncertainty

The cost comparison necessarily assumes that upadacitinib has similar long-term efficacy to ixekizumab and secukinumab. However, no robust long-term efficacy data was presented to support the assumption of long-term maintenance of treatment response on upadacitinib. As a first-in-class treatment in this indication, the validity of assuming equivalent long-term efficacy to bDMARDs is highly uncertain.

The ERG also notes that data on long-term real-world adherence to upadacitinib were not available (see Section 1.6). Due to the short biological half-life of upadacitinib relative to bDMARDs (hours vs. weeks), adherence issues may present a greater issue with regards to maintenance of response,

adherence issues leading to missed doses of upadacitinib due to may have a greater impact upon continuing efficacy, with potentially important implications for maintenance of response.

1.6 Long-term discontinuation: area of uncertainty

The cost comparison necessarily assumes that upadacitinib has the same long-term discontinuation due to AEs or loss of response as the comparators, ixekizumab and secukinumab. However, only very limited data on all-cause discontinuation was reported for upadacitinib. As a daily, orally administered therapy, barriers to treatment adherence will differ compared to monthly subcutaneous (SC) injections. Furthermore, loss of efficacy over time due to adherence issues or other uncharacterised reasons may lead to differences in long-term rates of discontinuation. The implications of differential rates of treatment discontinuation for the cost-effectiveness of upadacitinib can only be explored in a full cost-utility analysis, in order to capture downstream effects on costs and health outcomes. Therefore, the potential risk to the NHS if discontinuation on upadacitinib differs relative to the comparators, in either direction is uncertain, as the impact on costs and health outcomes is not captured in the cost comparison.

1.7 Time horizon: area of uncertainty

The most relevant time horizon for the cost comparison analysis is unclear due to uncertainty regarding the predicted duration of treatment with upadacitinib. Both the ERG and company's base case results are sensitive to the duration of the time horizon once the confidential prices of the comparators are considered.

1.8 Modelling the impact of adverse events

The cost comparison analysis does not include the costs associated with AEs for any of the treatments under comparison. The inclusion of these costs, as requested by the ERG at the clarification stage, would have allowed exploration of the uncertainty associated with the safety issues highlighted above for patients treated with JAK inhibitors. The ERG considers that, while the inclusion of AE costs in the cost comparison would have been appropriate, the issue remains that any potential differences in the incidence of AEs between upadacitinib and IL-17A inhibitors cannot be fully dealt with within the scope of a cost comparison FTA, and would require a cost-utility analysis to capture the impact of AEs on costs, health-related quality of life (HRQoL), and the consequences of discontinuing and switching treatment.

If the long-term safety profile of upadacitinib differs to that of the comparators, this exclusion would have uncertain implications for the relative cost-effectiveness of upadacitinib.

2 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

The ERG requested clarification on the company's proposed positioning of upadacitinib in the treatment pathway because this was unclear from the CS The company stated that from their clinician feedback the most relevant comparator for upadacitinib would be IL-17A inhibitors (both secukinumab and ixekizumab) in either the biologic-naïve or -experienced populations and that this was the basis of their clinical and cost comparison. The company's advisory board document, which reported clinician views on pathway position, stated in its summary that "*It was generally agreed that initially upadacitinib is likely to be prescribed as a second-line therapy, and with experience, clinicians may increase its use as a first-line therapy*".[1]

2.1 Relevant decision-problem according to NHS practice and the NICE scope

2.1.1 Population

The ERG's clinical advisers did not anticipate upadacitinib being used as a first-line treatment. This is because of an MHRA safety warning about another JAK inhibitor, tofacitinib (see Section 3.3), and concerns that this safety issue may extend to the JAK treatment class as a whole. The US Food and Drug Administration (FDA) also considers that all JAK inhibitors may pose similar safety risks,[2] which was also a concern raised by the ERG's clinical advisers. Nevertheless, the MHRA has not issued a safety warning about upadacitinib although the marketing authorisation for upadacitinib does advise that it should be used with caution in patients at high risk for VTE. One of the risk factors for VTE is obesity. The upadacitinib clinical study report (CSR) did not report on obesity levels using a 30kg/m^2 cut-off but a recent publication of a Spanish registry reported that 24% of AS patients were obese (>30kg/m^2).[3] Any overweight patients (body mass index (BMI) between 25 and 29.9kg/m^2) taking upadacitinib would need monitoring to check for the development of a VTE risk factor.

Given the uncertainty, both on the transferability of serious safety concerns about tofacitinib to this appraisal of upadacitinib and the guidance that upadacitinib should be used with caution in around a quarter of AS patients, the most relevant NHS population appears to be patients who have already taken a bDMARD (i.e. who are bDMARD-experienced, rather than bDMARD-naïve). One of the two upadacitinib trials (SELECT-AXIS 2) recruited only bDMARD-experienced patients so this trial population had the best applicability to the patients likely to receive upadacitinib in an NHS setting.

2.1.2 Comparators

Secukinumab and ixekizumab (in biologic-naïve and biologic-experienced patients) were the two comparators considered by the company in the CS. The company did not consider secukinumab 300mg to be a relevant comparator, and this dosage has also not been recommended by NICE.[4]

Therefore, when discussing the appropriateness of secukinumab as a comparator, the ERG refers specifically to secukinumab 150mg.

Page 7 of the CS stated that clinician feedback indicated that the clinical decision would centre on whether to use IL-17A inhibitors or upadacitinib, and therefore, upadacitinib would be used in the same place in the treatment pathway as IL-17A inhibitors. The ERG asked their two clinical advisers which bDMARD therapies they considered to be the most frequently used for AS in the NHS, across the various patient subpopulations and subgroups. Their responses, summarised in Table 1, portray variation in practice and also illustrate the importance of considering how best to treat any extra-articular manifestations when deciding on a treatment. Generally, a TNF-alpha inhibitor would be tried first, usually followed by either a second TNF-alpha inhibitor or an IL-17A inhibitor. Therefore, upadacitinib is unlikely to be prescribed in clinical practice for bDMARD-naïve patients. Sometimes all the treatment options within a therapy class would be tried before moving on to a treatment with a different mode of action. This may depend on extra-articular manifestations, on whether patients achieve initial treatment responses, which are eventually lost, or on whether they fail to achieve an initial response. The ERG's advisers thought that around 95% of patients would receive a TNF-alpha inhibitor as a first-line therapy, usually adalimumab or etanercept. Both advisers also considered secukinumab to have a small market share (around 5%) as a first-line therapy, explaining that they would only use it in patients with: a high risk of tuberculosis (TB); severe skin psoriasis (Psoriasis Area and Severity Index (PASI) >10, which is rare); personal or strong family history of multiple sclerosis; or suspicion of concomitant lupus. The company gave two estimates for secukinumab's first-line market share: [redacted] and [redacted] for and the market share in the bDMARD-experienced population: [redacted] or [redacted] (Section B.1.1.2.3, CS). These figures were derived from market research conducted in 2021, sampling a select number of clinicians treating AS patients. The company does not present estimates of market share for ixekizumab, stating that it has only recently be approved by NICE for AS and that there is an expectation that its share will increase over time. The ERG note that ixekizumab is not recommended by NICE as a first-line therapy (except in TNF-alpha inhibitor contraindicated patients) so it has an extremely small market share at first-line. As having a significant market share is one of the FTA process criteria to establish the relevance of a comparator, the ERG considers secukinumab to be the relevant comparator for bDMARD-experienced patients.

Clinical adviser views on the anticipated use and positioning of upadacitinib were also sought. Table 1 shows that for all patients except those with inflammatory bowel disease (IBD), the ERG's advisers did not anticipate upadacitinib being used before the third-line of treatment. These positionings for upadacitinib are based both on the level of confidence in the efficacy and safety profile of TNF-alpha inhibitors and IL-17A inhibitors, and on upadacitinib safety concerns about an increased risk of major adverse cardiovascular events (MACE), malignancies, serious VTE and infections (see Section 3.3).

The clinical advisers emphasised that variation in upadacitinib use would be expected, depending on the extent of concerns about the risk of serious adverse events (SAEs) and on how soon the use of a treatment with a new mode of action was deemed appropriate. Such judgements might be expected to vary across clinicians and by individual patient characteristics. The ERG considers that, from a clinical perspective, the most relevant comparators for upadacitinib at third-line of treatment are ixekizumab and secukinumab.

Table 1. ERG clinical adviser opinions on comparator use and the anticipated use of upadacitinib

Subpopulation or subgroup of AS patients	ERG clinical advisers' opinions on:	
	The comparators most likely to be used	The anticipated use of upadacitinib
bDMARD-naïve	Adalimumab or etanercept for most patients. In a smaller proportion of patients an IL-17A inhibitor may be considered.	Very unlikely to be used
bDMARD-naïve and contraindicated for TNF-alpha inhibitors	Secukinumab or ixekizumab	Very unlikely to be used
No response to first bDMARD (typically a TNF-alpha inhibitor)	Either try another TNF-alpha inhibitor or switch to secukinumab or ixekizumab	3rd line or later
Responded to first bDMARD (a TNF-alpha inhibitor) but lost response later	Either try another TNF-alpha inhibitor or switch to secukinumab or ixekizumab	3rd line or later
Subgroups of patients with extra-articular manifestations (estimated prevalence in patients with AS, based on a systematic review[5])		
Patients with a history of uveitis (23%)	Adalimumab (use etanercept with caution due to risk of exacerbating uveitis). If refractory, consider another TNF-alpha inhibitor such as golimumab, infliximab or certolizumab pegol. In a small proportion of patients an IL-17A inhibitor may be considered.	3rd line or later
Patients with active uveitis (6%)	Only adalimumab is licensed for active uveitis so it is used to tackle both conditions. If refractory, consider another TNF-alpha inhibitor such as golimumab, infliximab or certolizumab pegol. In a small proportion of patients an IL-17A inhibitor may be considered.	3rd line or later
Patients with psoriasis (10%)	Use adalimumab if psoriasis is moderate-to-severe, or etanercept if psoriasis is mild. Use infliximab, certolizumab pegol or an IL-17A inhibitor if refractory.	3rd line or later
Patients with IBD (4%)	IL-17A inhibitors are not recommended. Only infliximab, golimumab and adalimumab are licensed for IBD, so are preferred to etanercept.	2nd line or later

2.1.3 Impact of administration preference and medication adherence on pathway position

The CS (page 92) stated that there is a high unmet treatment need in AS for treatment options offering an alternative mechanism of action and mode of administration. The clinical advice to the ERG was that oral administration was unlikely to be an important advantage from the perspective of most AS patients, although it is very likely to be beneficial for needle-phobic patients. The ERG's advisers stated that it was unlikely that many patients would receive upadacitinib at an earlier line of treatment

as a result of being needle-phobic. In their experience very few patients were needle-phobic, and patients who disliked needles could tolerate monthly injections. The comparators secukinumab and ixekizumab, require only monthly maintenance injections, which, following a single initial training session from a healthcare professional, may be self-administered at home by the patient. As such these comparator treatments are thought unlikely to be much more burdensome to patients than a twice-daily oral option. Clinical advice to the ERG was also that an oral medication would unlikely be cost-saving compared to an injectable given that most patients self-administer the treatments after training, which is also often free of cost to the NHS.

However, clinical advice to the ERG was that adherence and compliance with a twice-daily tablet may possibly be problematic for some patients. Younger people of working age may forget to take a tablet during the day and older patients may have polypharmacy issues (i.e. they take too many tablets to remember to take them all). Compliance with upadacitinib 15mg was reported in the CSR for SELECT-AXIS 1 as [redacted] at 14 weeks follow-up, but longer-term follow-up data on compliance is not presented (data not available for SELECT-AXIS 2). Clinical monitoring of adherence to tablets is also likely to be more difficult than that of adherence to subcutaneously injected therapies. The ERG also notes that due to the biological half-life of upadacitinib, missed doses, treatment interruptions, and other issues leading to reduced adherence may cause the drug's efficacy to fluctuate compared to the less frequently administered SC biologics The ERG considers this to have been inadequately explored. In some situations, an immediate drop in drug levels after discontinuation may be an advantage, for example, the need for urgent discontinuation in response to a serious infection.

The need for an oral medication option for the treatment of AS may therefore be less pressing than the CS suggests, although it will be beneficial for the few patients who are needle-phobic.

2.2 Summary of ERG's view

In summary, although the company appears to suggest that upadacitinib might only displace secukinumab at the first-line of treatment, the ERG considers this comparator choice to be questionable in terms of market share and representativeness of therapies available at first-line. No clear clinical rationale was provided for not using a TNF-alpha inhibitor as a first-line comparator. Moreover, given the safety concerns described above, and the clinical advice received by the ERG, it is plausible that for most NHS AS patients (though not all), upadacitinib may be used as a new line of therapy (or it may displace a second IL-17A inhibitor). If upadacitinib were to be mostly used as a new line of therapy then the relevant comparator would be established clinical management without biologics, which was not mentioned in the NICE scope. In addition, this would not be a suitable comparator for the FTA process as it would not adequately represent the NICE recommended treatments as a whole in terms of cost and effects.

The introduction of an oral medication for treating AS is useful, although it is unlikely to change treatment decisions for the vast majority of AS patients.

3 SUMMARY OF THE ERG'S CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

3.1 Systematic review

3.1.1 Search strategy

The original CS included searches to identify clinical evidence studies for patients with AS. A detailed description of the searches and all search strategies were included in Appendix A (pages 179-209) and the update searches were included in Appendix B (pages 210-235).

In response to the ERG's clarification questions, a further document was provided by the company, which included additional search strategies and clarifications. The ERG's appraisal of the searches is reported in Table 2.

Table 2. ERG Appraisal of Evidence Identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	Extremely comprehensive. Additional update searches conducted on 28th October 2021 (mentioned in Document B, B.3.1, page 27) were not documented in the original CS but were provided by the company in their response to clarifications.
Were appropriate sources searched?	YES	An excellent range of relevant databases, conference proceedings, grey literature sources and trials registry databases were used.
Was the timespan of the searches appropriate?	YES	No publication date limits were placed on any of the searches. The (first) update searches were performed in late March 2021.
Were appropriate parts of the PICOS included in the search strategies?	YES	Population AND Intervention AND Study Type
Were appropriate search terms used?	YES	Search terms are extremely comprehensive and designed very carefully. Although the condition synonym rheumatoid spondylitis was not included, this is unlikely to have made any difference to the results of the searches. Terms for some of the biosimilars were not used in the clinical searches: Adalimumab: Kromeya, Solymbic, Yuflyma, PF-06410293 Etanercept: Nepexto, BX2922, Etacept, Etanar, GP2013, PRX-106, Yisaipu, Eticovo, Lifmior This was raised as a question at the clarification stage. In their response to clarifications, the company re-ran the searches but found no additional evidence eligible for inclusion.
Were any search restrictions applied appropriate?	YES	Animal studies and irrelevant paper types were removed appropriately. The sponsor requested that the LILACS database was limited to English language and this was queried by the ERG at the clarification stage. In their response to clarifications, the company re-ran the searches on this database without this limit and found no additional evidence.

Were any search filters used validated and referenced?	YES	Various search filters were used and referenced, although there was no mention of whether filters were validated.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

3.1.2 Study selection and data extraction

A systematic literature review was conducted to identify clinical and non-clinical evidence pertaining to the bDMARD-naïve and -experienced patients, reported in Appendix C of the CS.

The inclusion criteria are presented in Table 1 of the CS. All relevant interventions/ comparators measures listed in the NICE scope were included. Studies including populations with non-radiographic axial spondyloarthritis (axSpA) were excluded. Clinical advice to the ERG was that subclassifying AS and non-radiographic axSpA patients remains relevant as their response to therapies may be different and not all non-radiographic axSpA patients progress to AS. Therefore, the ERG considers this to be appropriate and note that it is in line with the NICE scope and previous appraisals.[6]

Although not explicitly excluded, outcomes of extra-articular manifestations including uveitis, inflammatory bowel disorder (IBD) and psoriasis are not listed in the review's inclusion criteria but are listed within the NICE scope. Clinical advice to the ERG was that decisions regarding which bDMARD to offer are sometimes influenced by their likely impact on extra-articular manifestations of AS.[7] Therefore, the ERG notes that it may have been useful to identify any relevant clinical evidence that reported on these outcomes to facilitate comparison with other interventions used to treat AS.

Stand-alone safety studies and systematic reviews were excluded. Given the safety concerns by the FDA and MRHA regarding the JAK inhibitor tofacitinib (which may be common to all JAK inhibitors – see section 3.3 for further detail), the ERG believe it would have been appropriate to include these study types so that potentially relevant evidence regarding the safety of upadacitinib in populations other than AS (e.g. rheumatoid arthritis (RA) patients), the safety of other JAK inhibitors (e. g. tofacitinib)[8] and comparator interventions relevant to this appraisal (e. g. secukinumab)[9] could be considered.

Languages other than English were also tagged during title–abstract screening, and did not move forward to full-text screening. Therefore, there may be relevant studies in non-English language that were not included in the evidence synthesis.

Appropriate methods were used to select studies for inclusion and to reduce reviewer error and bias with two reviewers conducting the screening of literature independently and any discrepancies

resolved with assistance from a third reviewer. Data extraction methods were also appropriate with one reviewer extracting the data and another auditing the data extraction for accuracy and completeness.

3.1.3 Quality assessment

The methods of quality assessment are reported in sections 4.1.5 and 4.2.5 Appendix C of the CS. The company use the minimum criteria recommended by NICE[10] for assessment of risk of bias and generalisability in parallel group randomised controlled trials (RCTs). For non-randomised studies, the CS does not state which domains were assessed. The company report the quality assessment results for clinical and non-clinical studies in Appendix G and H, respectively, of Appendix C. However, only the judgements for each criterion were reported (and limited justification for these choices) and not an overall risk of bias judgement for each study. No action beyond reporting the results of the quality assessment was taken for clinical studies of uncertain or high risk of bias. The ERG note it would be useful for the company to have discussed any potential impact of bias on the clinical effectiveness evidence.

3.2 Clinical effectiveness of upadacitinib

Clinical effectiveness evidence on the use of upadacitinib 15mg to treat AS comes from two RCTs, SELECT-AXIS 1 and SELECT-AXIS 2, described in section B.3.2 in the CS.

3.2.1 Clinical trial population

SELECT-AXIS 1 includes a bDMARD-naïve population who have inadequate response to at least two non-steroidal anti-inflammatory drugs (NSAIDs) or contradictions to NSAIDs. SELECT-AXIS 2 includes a bDMARD-experienced population, previously treated with 1 or 2 bDMARDs, which they discontinued due to lack of efficacy or intolerance. Both studies compare upadacitinib with placebo.

The inclusion criteria for SELECT-AXIS 1 and SELECT-AXIS 2 are reported in Tables 10 and 17 of the CS, respectively. Clinical advice to the ERG was that the inclusion criteria for both trials are broadly appropriate and relevant to patients seen in NHS practice. Both SELECT-AXIS 1 and SELECT-AXIS 2 exclude patients with extra-articular manifestations that are not clinically stable for at least 30 days prior to study entry. Clinical advice was that this is normal for clinical trials within this disease area and would likely be the same for other clinical trials included in the NMA presented in the CS. In clinical practice it might be a reason to start a particular bDMARD which may be more effective for treating particular extra-articular manifestations.

The baseline characteristics of the SELECT-AXIS 1 trial population are reported on page 42 (Table 13) and the SELECT-AXIS 1 trial population on page 54 (Table 20) of the CS. Clinical advice to the

ERG was that these characteristics are broadly representative of what would be seen in practice in the NHS. The ERG requested for each trial the number and proportion of patients taking NSAIDs, corticosteroids and conventional synthetic DMARDS (csDMARDs) at (1) randomisation and (2) at weeks 0, 4, 8 & 14, however the company explained in their clarification response that these data are only available at baseline (a limitation of the clinical trial design). It is therefore, unclear the proportion of patients who remained on these therapies throughout the trial and any impact this may have had on the efficacy results.

3.2.2 Methods of SELECT-AXIS 1 and SELECT-AXIS 2

Statistical methods used are reported in Table 11 of the CS for SELECT-AXIS 1 and Table 18 for SELECT-AXIS 2 and are appropriate to address the questions of the efficacy of upadacitinib for treating AS. The primary outcome of both the SELECT-AXIS 1 and SELECT-AXIS 2 trials is the number of patients with at least 40% improvement in the Assessment of SpondyloArthritis International Society scale (ASAS40) response at 14 weeks. Clinical advice to the ERG was that in the United Kingdom (UK), the number of patients with at least 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50) is the most useful clinical benchmark.

3.2.3 Clinical trial results

Efficacy results for key primary and secondary end-points are reported for SELECT-AXIS 1 in section B.3.6.1.6 of the CS and for SELECT-AXIS 2 in section B.3.6.2.6 and include multiplicity adjusted results (Tables 15 and 21, respectively). The ERG requested the inclusion of BASDAI change from baseline in these tables, which the company provided in their response to clarification. These results were in line with that seen in clinical trials of comparator treatments for both bDMARD-naïve and -experienced populations.[11-13].

Figure 4 in the CS shows ASAS40 response rate over time in SELECT-AXIS 1 indicating that this continues to increase from weeks 12-14. As randomised evidence is not available past 14 weeks, it is not clear at what point treatment efficacy plateaus. The European public assessment report (EPAR) for upadacitinib states that patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.[14] For SELECT-AXIS 2 the corresponding figure (Figure 6) is missing from the CS, so the ERG are unable to comment on this for the bDMARD-experienced population. A key area of uncertainty for both bDMARD-naïve and -experienced populations is the longer-term efficacy of upadacitinib and the length of time patients may sustain a response to treatment. Clinical advice to the ERG was that, in principle, patients would not develop antibodies to JAK inhibitors, as they are small molecules, and therefore, an initial response would be sustained. Although, they add there is insufficient evidence to speculate on long-term effectiveness of upadacitinib and the similarities with JAK inhibitors and bDMARDs.

Extra-articular manifestations were not reported at 14 weeks follow-up in either SELECT-AXIS 1 or SELECTI-AXIS 2. As it would be useful to see how upadacitinib affects extra-articular manifestations at the clarification stage, the ERG requested the number and proportion of patients with extra-articular manifestations in the upadacitinib trials. The company explained these data were only collected at baseline, but it was observed that no new cases of uveitis or IBD were observed in the upadacitinib arm over 64-week follow-up (13 events of uveitis in 8 patients were observed in patients with a history of the condition).

Subgroup analyses

Subgroup analyses are reported only for SELECT-AXIS 1 in section B.3.7 of the CS and only for the main outcome of ASAS40 for which treatment effects are reported to be in favour of upadacitinib compared to placebo. Effect estimates and/or statistical significance for these analyses are not included in the CS, although an updated CSR provided in response to clarification includes forest plot of ASAS40 response rate at week 14 by subgroups. Subgroup data on change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) C-reactive protein (CRP) and BASDAI50 at week 14 is also reported in a conference abstract.[15] There is some evidence that gender, AS symptom duration < 5 years, and baseline CRP levels may influence outcomes and therefore, the ERG note the uncertainty around how effective upadacitinib 15mg would be for these patients when treated in clinical practice. For the bDMARD-experienced population, the ERG is unable to comment on the efficacy of upadacitinib 15mg in pre-specified subgroups as the data are not yet available for this trial.

3.2.4 Network meta-analyses

The company provide a summary of the clinical effectiveness evidence for bDMARD-naïve populations, bDMARD-experienced populations, combination bDMARD-naïve and -experienced populations and populations with unknown bDMARD treatment history in appendix C of the CS. A brief summary of safety data from the included trials is also reported. Clinical effectiveness evidence is synthesised using NMAs.

3.2.4.1 Previous Appraisals for Treatments in Ankylosing Spondylitis

Previous appraisals in AS have conducted NMAs to evaluate the relative efficacy and safety of TNF-alpha inhibitors (TA383), secukinumab (TA407) and ixekizumab (TA718) compared to other available bDMARDs. The methods used for the NMAs for the upadacitinib appraisal were broadly similar to the approaches used in previous appraisals, but there were some differences.

Population

The company conducted NMAs in bDMARD-naïve and bDMARD-experienced populations. NMAs including all relevant RCTs where the majority of patients were bDMARD-naïve and including only

data on bDMARD-naïve patients were carried out (see Table 9, in Appendix 1 for a summary of the NMAs conducted by the company).

The company's approach to modelling the population is similar to the ixekizumab appraisal (TA718), where bDMARD-naïve and bDMARD-experienced patients were modelled separately. They also conducted sensitivity analyses which included trials where the population of interest was unclear, or where there was a mixed population where the outcomes were not reported separately. In TA407 (secukinumab), the NMAs modelled a mixed and a bDMARD-naïve population. The trials included in the multiple technology appraisal (MTA) on TNF-alpha inhibitors (TA383) had mixed populations (with the majority of patients being bDMARD-naïve).

Time point of Assessment of Outcomes

There is heterogeneity in the time point of assessment of initial response across the trials included in the current and previous appraisals, ranging from 10-16 weeks. In previous appraisals, ERGs have considered that this approach could introduce uncertainty into the model. It has been suggested that response rates may be higher in the trials where response is measured later, as the patients have a longer period to respond to their treatment (as discussed in TA407 and TA718).

In the upadacitinib NMAs, outcomes were assessed at pooled week 12-16 timepoints, with a preference for timepoints closest to week 12. The company present different NMAs, where the time point of outcome assessment for upadacitinib is modelled at week 12 and week 14 (see Table 9 in Appendix 1 for further information). The company consider that a week 14 time point of outcome assessment to be most appropriate and present that in the main CS (NMAs using week 12 time point of outcome assessment are presented in Appendix D). The ERG agrees that the NMA models using week 14 data for the bDMARD-naïve and bDMARD-experienced populations are the most appropriate to assess the effectiveness of upadacitinib compared to secukinumab and ixekizumab. The SmPC for upadacitinib suggests discontinuation if there is no response by 16 weeks, and therefore, the ERG would consider a 16-week data cut to be ideal to compare upadacitinib to other interventions within the NMA.[14] However, the length of the placebo-controlled period in each trial for upadacitinib 15mg is limited to 14 weeks, and so the randomised evidence at 16 weeks is not suitable for inclusion in the NMA.

The single technology appraisals (STAs) of secukinumab (TA407) and ixekizumab (TA718) used a similar approach and pooled the different time points of response assessment from the included trials, which ranged from 12 to 16 weeks. The MTA of TNF-alpha inhibitors also pooled the responses assessed at weeks 10-16.

Selection of outcomes

NMAs were conducted for several outcomes, including some not considered in previous appraisals (Table 3).

Table 3. Outcomes included in the NMAs in the upadacitinib appraisal and previous appraisals for ankylosing spondylitis

Upadacitinib (this appraisal)	TNF-alpha inhibitors (TA383)	Ixekizumab (TA718)	Secukinumab (TA407)
ASAS20 ASAS40 BASDAI50 BASDAI score CFB BASFI score CFB ASASPR Total Back Pain score CFB	BASDAI50 BASDAI score CFB BASFI score CFB	ASAS20 ASAS40 BASDAI50 BASDAI score CFB BASFI score CFB	ASAS40 BASDAI50 BASDAI score CFB BASFI score CFB

ASASPR: Assessment of ankylosing spondylitis – partial remission; BASFI: Bath Ankylosing Spondylitis Functional Index; CFB: Change from baseline

The company considered ASAS40, BASDAI50, BASDAI CFB, and Bath Ankylosing Spondylitis Functional Index (BASFI) CFB key outcomes and presented the results for these outcomes for the company's preferred models in Section B.3.9.2 of submission Document B. The company's key outcomes are consistent with the key outcomes assessed in previous appraisals TA383, TA407, and TA718. Complete results for the key outcomes as well as ASAS20 and Assessment of ankylosing spondylitis – partial remission (ASASPR) were presented in Appendix D for transparency. The company did not conduct any NMAs for quality of life (QoL) or AEs outcomes.

The company presents a cost comparison analysis under the assumption that upadacitinib has similar efficacy to secukinumab and ixekizumab for all outcomes considered relevant in previous appraisals.

Fixed/Random Effects Models

The company provided results of both fixed and random effects NMA models. The company provided clarification that the fixed effect (FE) models (provided in the main CS) are the most appropriate and should be used for decision making as they are favoured by model selection statistics and as there is no reason to expect substantial heterogeneity in the included studies. The random effects (RE) models (presented in the CS, Appendix D) were only considered for completion.

Previous appraisals have also favoured FE models. The STA of ixekizumab (TA718) and secukinumab (TA407) only presented FE models. The MTA of TNF-alpha inhibitors used both FE and RE models in the NMAs, but the FE models were preferred.

Placebo or Baseline-Adjustment

The company also explored placebo adjustment in both FE and RE models. However, due to data sparsity these models did not converge for the bDMARD-experienced population. In the bDMARD-naïve population, placebo-adjusted models were selected for the ASAS40 and BASDAI score CFB outcomes. On inspection of the regression plots provided in response to clarification question A16, the adjusted models appeared plausible.

Placebo-response adjustments were also explored in previous appraisals (TA407 and TA383) but were often not appropriate, particularly in RE models due to data sparsity.

Class Effect

The MTA of TNF-alpha inhibitors for AS explored whether the data supported an assumption of a class effect across TNF-alpha inhibitors; that is, that these treatments can be assumed to be similarly effective. The STA of secukinumab (TA407) did not discuss class effects for IL-17A inhibitors but after the technical engagement process in the ixekizumab appraisal (TA718), the company considered it reasonable to assume a class effect for all biologic treatments for axSpA and to assume equivalent efficacy across TNF-alpha inhibitors and IL-17A inhibitors. However, the committee deemed this to be inappropriate and concluded that a class effect had not been established for all TNF-alpha inhibitors and IL-17A inhibitors.[16]

In the original CS, the company did not consider an NMA assuming class effects for IL-17A inhibitors. At clarifications, the ERG also asked the company to comment on the plausibility of a class effect for effectiveness and safety across other JAK inhibitors (including tofacitinib and filgotinib). Owing to the paucity of head-to-head or indirect treatment comparisons between JAK inhibitors, the company did not consider it appropriate to assume there is a class effect for efficacy or safety.

3.2.4.2 Studies included in the NMA

A list of the studies included in each NMA for secukinumab (150mg) and ixekizumab (80mg every 4 weeks (Q4W)) is presented in Table 10, Appendix 1. For the bDMARD-naïve population, one study each provided the evidence for upadacitinib and ixekizumab. A bDMARD-naïve subgroup from the MEASURE studies supplied evidence on secukinumab. The MEASURE studies did not report all outcomes: there was no secukinumab comparator for BASFI CFB, and only one study (MEASURE 2) reported data for BASDAI50.

The NMA for bDMARD-experienced patients only compared upadacitinib to ixekizumab. The five MEASURE trials that reported the efficacy of secukinumab were excluded by the company as only a small population of patients in these trials were bDMARD-experienced. Additionally, the patient inclusion criteria for MEASURE 1 and 2 were different from SELECT-AXIS 2, and the patient populations were not strictly comparable. The company's clinical advisors expect the comparison

between the efficacy of upadacitinib and secukinumab to be similar in the bDMARD-naïve and bDMARD-experienced populations. The ERG's clinical advisors had reservations about this claim, as treatment benefits tend to fall after a patient has had experience with a bDMARD, but it is naïve to assume that the decrease in treatment effect would be similar in upadacitinib (a JAK inhibitor) and secukinumab (as IL-17A inhibitor) as both drugs have different mechanisms of action.

3.2.4.3 Potential Causes of Heterogeneity in the NMAs

The company provide a comprehensive description of the baseline characteristics of the included studies (Appendix D: Sub-Appendix B, Table 72 and Figures 32 to 47). Overall, the majority of baseline characteristics are relatively similar across the included studies, especially for trials of bDMARD-experienced patients; however, there are some differences across the trials for baseline CRP levels and age.

CRP levels are a marker of systemic inflammation, and elevated CRP levels are a predictor of clinical response to treatment.[17] For bDMARD-naïve patients, there are substantial differences in baseline CRP levels across the studies included in the NMA (Appendix D, Figure 38). In the SELECT-AXIS 1 trial, mean CRP level at baseline was considerably less ([redacted] mg/L in upadacitinib arm, [redacted] mg/L in placebo arm) than the overall mean CRP level across all trials ([redacted] mg/L). This could introduce heterogeneity into the network, as the CRP level in that study is less than the 14mg/L threshold that was discussed in TA383 as being a key predictor of treatment response.[18, 19] However, in TA718 it was noted that while the variation in CRP levels may introduce heterogeneity, there is no evidence to suggest that this would bias the relative treatment effects in favour of any particular treatment.

For bDMARD-experienced patients, baseline CRP levels in SELECT-AXIS 2 are relatively similar to the other studies included in the network (Appendix D of the CS, Figure 39).

Furthermore, there is some variation in baseline age in the bDMARD-naïve patients included in the network. While the majority of studies have ages that are fairly similar, the mean age of participants in some trials is substantially older, or younger than the mean, which could introduce heterogeneity into the network. Patients in SELECT-AXIS 1 were considerably [redacted] ([redacted] years in the upadacitinib arm, and [redacted] years in the placebo arm, Figure 32, and Table 72 of Appendix D of the CS), than the overall mean ([redacted] years). As younger age was found to be an independent predictor of treatment response, effectiveness estimates for upadacitinib may be conservative.[20, 21] For bDMARD-experienced patients, baseline ages across the trials are relatively homogenous, with the exception of MEASURE 5, where the patients were [redacted] years (in the secukinumab arm).

The company also considers that while time since diagnosis of AS is comparable for the majority of the trials included in both NMAs, the SPINE study has a longer time since diagnosis (~20 years) compared to the other studies in the biologic-naïve/mixed network.

For most of the baseline characteristics, two trials of adalimumab with bDMARD-naïve patients (Huang, 2014[22] and Hu, 2012[23]) are consistent outliers. Participants included in these trials were considerably younger, had higher levels of CRP at baseline, a higher proportion of patients who were human leukocyte antigen-B27 (HLA-B27) positive, and had lower baseline BASFI scores compared to the overall mean (Appendix D, Figures 32, 38, 40 and 42), all of which are predictors of response for patients with AS.[24] Despite these differences, the trials include relatively few patients and provide only limited indirect evidence on the comparison of upadacitinib to ixekizumab, and therefore are unlikely to have any meaningful impact on the results.

Overall, the ERG agrees with the company that there is minimal cross-study heterogeneity with regards to the baseline characteristics of the studies included in the NMAs.

3.2.4.4 Results of the NMAs presented in the company submission

The company conducted an NMA to compare the relative efficacy of upadacitinib to secukinumab and ixekizumab, the two comparators considered most relevant in bDMARD-naïve and bDMARD-experienced populations. NMAs were conducted for the outcomes described in Table 3.

bDMARD-naïve population

The company preferred baseline-risk adjusted or unadjusted RE models for some outcomes. However, the ERG believes that simpler models could be selected. When the difference between the deviance information criteria (DICs) for competing models was also less than three units, the ERG selected the simpler model as recommended by the NICE Decision Support Unit (DSU) Technical Support Document (TSD)2.[25] Additionally, as there were few studies per comparison in the network for each outcome, there likely is insufficient evidence to adequately estimate the between study heterogeneity for many of the outcomes, hence the width of the confidence interval (CI) may be overestimated.[26-28]

In response to clarification question A19, the company provided forest plots comparing the results for all models fitted to each outcome. These demonstrated that the overall clinical effectiveness conclusions are unchanged regardless of the model fitted.

Results for the ERG-preferred NMA models for the bDMARD-naïve populations are presented in Table 4. The credible intervals (CrI) for all outcomes crossed the null effect, so there was insufficient evidence to suggest a difference in treatment effect between upadacitinib compared to either secukinumab or ixekizumab. Although the point estimates appear to suggest that upadacitinib is little

less efficacious than ixekizumab, results are very uncertain. The results for the ASAS40 FE model were consistent with the RE model.

Table 4. Results of ERG-preferred models for bDMARD-naïve patients for week 14 efficacy outcomes (NMA 3)

Outcome	Selected Model	Number of Studies	Upadacitinib vs. Secukinumab (SEC 150)	Upadacitinib vs. Ixekizumab (IXE80Q4W)
			OR (95% CrI)[a]	
ASAS40**	FE	14	[redacted]	[redacted]
	RE	14	[redacted]	[redacted]
BASDAI50	FE	10	[redacted]	[redacted]
			MD (95% CrI)[b]	
BASDAI CFB	Baseline-risk adjusted FE	16	[redacted]	[redacted]
BASFI CFB	FE	12	[redacted]	[redacted]

[a] null effect is 1; [b] null effect is zero. * Secukinumab was not included in the network for BASFI CFB. ** Unclear which should be the preferred model.

Abbreviations: CFB: change from baseline, CrI: credible interval, FE: fixed effect, MD: mean difference, OR: odds ratio, RE: random effects.

bDMARD-experienced population

The networks for the bDMARD-experienced population were very sparse – only two studies (COAST-W and SELECT-AXIS 2) were included in the NMA for all outcomes. The company selected FE models for all outcomes. The ERG agrees with the models chosen by the company, and results are presented in Table 5.

The CrIs for the estimates for all outcomes crossed the null effect, therefore, there was insufficient evidence to suggest a difference in treatment effects between upadacitinib compared to ixekizumab. The company also presented a scenario in Appendix G (Sections 7.2 and 7.5) that included all relevant secukinumab evidence (see Section 3.2.4.2). The results of these alternate NMAs were broadly consistent with the results for secukinumab and ixekizumab presented in Table 5. However, for the bDMARD-experienced population upadacitinib was favoured in comparison to ixekizumab when the baseline-risk adjusted FE model was selected for (ASAS40).

Table 5. Results of ERG-preferred models for bDMARD-experienced patients for week 14 efficacy outcomes (NMA 5)

Outcome	Selected Model	Number of Studies	Upadacitinib vs. Ixekizumab (IXE80Q4W)
			OR (95% CrI)[a]
ASAS40	FE	2	[redacted]
BASDAI50	FE	2	[redacted]
			MD (95% CrI)[b]
BASDAI CFB	FE	2	[redacted]
BASFI CFB	FE	2	[redacted]

[a] null effect is 1; [b] null effect is zero.

Abbreviations: CFB: change from baseline, CrI: credible interval, FE: fixed effect, MD: mean difference, OR: odds ratio

3.3 Safety of Upadacitinib

3.3.1 Safety evidence in AS and other indications

The CS (page 84) reported that "*the safety profile of upadacitinib is similar to that observed with [TNF-alpha inhibitors] and IL-17A inhibitors for the treatment of AS"*. Although the number of SAEs were low and roughly balanced across groups in the two upadacitinib AS trials, the ERG's clinical advisers alerted the ERG to ongoing concerns about the safety of another JAK inhibitor, tofacitinib, explaining that the MHRA had issued safety updates in 2020 and 2021 warning that, unless there are no suitable treatment alternatives, tofacitinib should not be used in patients with any of the following risk factors: being over 65 years of age, current or past smokers, VTE risk factors, cardiovascular (such as diabetes or coronary artery disease) risk factors or malignancy risk factors.[29, 30] In addition to the MHRA warnings, the U.S. FDA required revisions to the Boxed Warning, the FDA's most prominent warning, for tofacitinib, baricitinib and upadacitinib to include information about the risks of serious heart-related events, cancer, blood clots, and death.[2] The FDA considers that all JAK inhibitors may pose similar safety risks to those seen for tofacitinib. Upadacitinib is also a JAK inhibitor and so the ERG's clinical advisers would prefer to exercise caution in case upadacitinib has similar safety risks.

The SmPC also advises that upadacitinib should be used with caution in patients at high risk for VTE. As mentioned in Section 2, one of the risk factors is obesity and around a quarter of AS patients may be obese (BMI>30kg/m^2). Other patients may develop VTE risk factors whilst taking upadacitinib so it is evident that a cautious approach is needed when making a decision to prescribe upadacitinib.

In light of these issues, the ERG asked the company to comment on the possibility of a class safety effect across JAK inhibitors based on the FDA's warnings. The company stated that the FDA recognises that upadacitinib and baricitinib have not been studied in trials similar to the tofacitinib safety trial but since they share mechanisms of action with tofacitinib, the FDA believes they may have similar risks. The company added that this communication was not based on any safety data for upadacitinib, which does not show increased risks of these events and that in the absence of direct head-to-head JAK inhibitor studies, the benefit-risk (efficacy and safety) profile of one JAK inhibitor cannot be extrapolated to the entire JAK inhibitor class. The company also listed and described its safety studies in other indications. These indicated that upadacitinib had a good safety profile, although the ERG notes that none were head-to-head randomised safety studies, nor appeared to be designed/powered for safety outcomes. Whilst the ERG acknowledges the points made by the company, the evidence presented does not appear to be robust enough to fully allay concerns that there may be a class safety effect. Moreover, the ERG notes that a class safety effect has already been observed insomuch that upadacitinib, filgotinib, baricitinib and tofacitinib all have special warnings

and precautions for use with their SmPCs stating that they should be used with caution in patients with risk factors for deep venous thrombosis and pulmonary embolism.

3.3.2 Upadacitinib discontinuation rates

Discontinuation of upadacitinib 15mg due to AEs is reported for the SELECT-AXIS 1 study, as [redacted] at 14 weeks follow-up and [redacted] at 104 weeks follow-up (Tables 4 and 6 of the CSR). This is consistent with that demonstrated in clinical trials of upadacitinib for other indications including psoriatic arthritis and RA.[31] For SELECT-AXIS 2 data are only reported at 14 weeks follow-up as [redacted] (Table 1 of the CSR). Discontinuation due to lack of efficacy is only reported for the SELECT-AXIS 1 study at 104 weeks follow-up ([redacted] (Table 6 of CSR) and SELECT-AXIS 2 study at 14 weeks follow-up ([redacted] (Table 1 of CSR).

3.3.3 Network meta-analyses of safety and discontinuation outcomes

Despite the ERG's request at the clarification stage to conduct a synthesis of discontinuation rates due to AEs, AEs and SAEs of upadacitinib versus IL-17A inhibitors, the company stated that based on clinician feedback that the safety profiles of upadacitinib and IL-17A inhibitors are comparable. Previous appraisals of secukinumab (TA407), ixekizumab (TA718) or TNF-alpha inhibitors (TA383) also did not conduct safety NMAs. The company instead presented tables of naïve safety data comparisons with secukinumab and ixekizumab. These suggested the SAE rates were similar at timepoints up to two years, although the number of events was often small (which meant meaningful comparisons were not possible).

3.4 Summary of ERG's view

The clinical trial evidence submitted had sufficiently robust internal validity and its applicability to the NHS was acceptable. The company conducted NMAs to compare the relative efficacy of upadacitinib to the IL-17A inhibitors secukinumab and ixekizumab in bDMARD-naïve and bDMARD-experienced populations. There was no evidence to suggest a difference in the treatment effects of upadacitinib compared to secukinumab and ixekizumab. However, due to the sparsity of the networks, especially for bDMARD-experienced patients, there was a high level of uncertainty in the estimates, particularly for ASAS40 and BASDAI50. The company did not conduct NMAs on QoL or safety outcomes. The company fitted several different NMA models but overall, results were similar for all models explored.

Although the short-term safety and discontinuation data for upadacitinib appear favourable, long-term safety data for AS patients are not available. Given the extent to which the upadacitinib SmPC advice on cautionary use affects the AS population, and the uncertainty about a JAK inhibitor class effect for

cardiovascular and malignancy events, there are grounds to doubt the claim for similarity of safety outcomes when compared with bDMARDs.

4 SUMMARY OF THE ERG'S CRITIQUE OF COST EVIDENCE SUBMITTED

The appropriateness of assessing the cost-effectiveness of upadacitinib in the context of a cost comparison FTA relies on the validity of the assumption of equivalent efficacy (see Section B.3.9, CS) and safety (adherence and discontinuation) (see Section 3.3) of upadacitinib to at least one relevant comparator. Under the assumption that it is appropriate for this appraisal to proceed as a cost comparison FTA, the ERG seeks to identify the set of assumptions under which upadacitinib is likely to be cost saving or equivalent in cost to the selected comparator.

The ERG also highlights throughout the subsequent subsections, features of the cost comparison that may be affected by uncertainty surrounding the validity of assuming equivalent efficacy and safety of tofacitinib to at least one relevant comparator.

4.1 Company cost comparison

4.1.1 Summary of cost comparison

The company presents a cost comparison analysis considering upadacitinib 15mg as an alternative treatment to secukinumab 150mg per month and ixekizumab 80mg Q4W.

The costs included in the cost comparison are drug acquisition (Section B.4.2.2, CS), administration costs (Section B.4.2.3, CS), and monitoring costs (Section B.4.2.3, CS). Costs were estimated over a 5-year time horizon, with scenario analyses presented for time horizons of two, nine, and ten years. All costs are expressed in 2019/20 prices and undiscounted. The company considers that upadacitinib can be used as first or subsequent line of therapy, but does not present separate results for bDMARD-naïve and -experienced patient populations. A summary of resource use and costs applied in the company's cost comparison are summarised in Table 6. A brief description of the parameterisation and assumptions of the cost comparison are presented in the following sub-sections.

The company did not consider a comparison with secukinumab 300mg to be relevant (see Section 2.1.2), and did not submit a version of the electronic model parameterised with this dosing schedule, the ERG therefore focuses on the 150mg dosing schedule throughout the following sections.

Table 6. Summary of costs in the cost comparison analysis

	Upadacitinib	Ixekizumab	Secukinumab
Dose	15mg once daily	160 mg loading, then maintenance 80 mg Q4W	150mg per week for 5 doses, then 150mg per month.
Mode of administration	Oral	SC injection	SC injection
Drug acquisition unit cost	Rinvoq (15mg, pack of 28): £805.56 (list price), £337.30 [redacted](PAS price)	Taltz 80mg/1ml solution for injection pre-filled pens (pack of 1), £1,125.00 (list price)	Cosentyx 150 mg per 1 ml - pre-filled disposable injection (pack of 2), £1,218.78 per pack (list price)
Annual drug acquisition cost	£10,508 (list price) [redacted] (PAS price)	Year 1: £16,338 Subsequent years: £14,675	Year 1: £9,750 Subsequent years: £7,313
Total acquisition drug costs	£40,403 (list price), [redacted] (PAS price)	£58,095	£30,554
Administration cost	£0	£48 at first dose	£48 at first dose
Monitoring costs	1st year: £724.73 Subsequent years: £328.32/year	1st year: £724.73 Subsequent years: £328.32/year	1st year: £724.73 Subsequent years: £328.32/year

Q4W, every 4 weeks; PAS, patient access scheme; SC, subcutaneous.

4.1.1.1 Acquisition costs

Acquisition costs for upadacitinib are presented for the drug's list price and with a PAS, consisting of a simple discount of [redacted] on the list price from the British National Formulary (BNF) 2021.[32] The comparators' acquisition costs are based on their list prices as sourced from the BNF, 2021.[32] The company acknowledges the existence of confidential PAS discounts offered to the NHS for both comparators, but these are not included in the company's base case analysis as they are not publicly available. The ERG presents drug acquisition costs and results reflecting the comparator PAS prices in a separate confidential appendix. The annual and total drug acquisition costs in Table 6, assume the dosing schedules stipulated in the intervention and comparators' SmPCs. The company's analysis does not consider the effect of dose interruptions or adjustment upon acquisition costs.

4.1.1.2 Administration costs

SC administration of drugs is assumed to be undertaken by the patient following a one-off training by a band 6 nurse; only the cost of nurse time is included in the analysis, in line with TA383.[33] The company states that the unit cost of training corresponds to the time of one hour of a band 6 nurse (£48.00) according to Personal Social Services Research Unit, (PSSRU) 2019.[34] The setting in which this training is assumed to be delivered in the CS is unclear and therefore the ERG could not validate this cost.

In response to a request from the ERG, the company also provided a scenario analysis in which self-injection training is assumed to have already taken place or is otherwise provided free of charge to the NHS.

4.1.1.3 Monitoring costs

Monitoring resource use (see Table 35, CS, for details) is assumed to be the same for all interventions under comparison and is sourced from previous appraisals in AS.[4, 18, 35] Resource use and costs associated with monitoring are higher in the first year in the model for all treatments compared to subsequent years, due to more intensive monitoring in the initiation period (first three months of treatment) compared to the subsequent maintenance period.

4.1.1.4 Treatment discontinuation rates

The company's base case analysis assumed that rates of discontinuation were equal across the modelled treatments, adopting an annual discontinuation probability of 11% (applied as 2.87% per 3-month cycle), in line with preferred assumptions in previous technology appraisals (TAs).[4, 16, 33] Patients were assumed to incur no further costs following treatment discontinuation.

CS Section B.4.4 presents three alternative scenario analyses considering treatment discontinuation. Scenario 1 applied an annual discontinuation rate of 6.57% to all treatments (11% in the base case) based on a 2018 study of first-line TNF-alpha inhibitors in AS.[36] Scenario 2 applied a discontinuation rate of 11.84% to all treatments, reflecting second-line TNF-alpha inhibitors in the same study. Scenario 3 applied differential rates of discontinuation across the three treatments based on data from their respective pivotal trials. Upadacitinib and ixekizumab trial data were only used to model discontinuation for the first year, with rates assumed to drop to those of secukinumab for all subsequent years. See Table 7 for the discontinuation rates applied in the company's analysis.

Table 7. Discontinuation rates modelled in the company's cost comparison

Scenario	Upadacitinib			Ixekizumab			Secukinumab		
	Month 1-3	Per 3-month cycle		Month 1-3	Per 3-month cycle		Month 1-3	Per 3-month cycle	
		Year 1	Year 2+		Year 1	Year 2+		Year 1	Year 2+
Base case	2.87%			2.87%			2.87%		
Scenario 1	1.68%			1.68%			1.68%		
Scenario 2	3.10%			3.10%			3.10%		
Scenario 3	2.76%	4.21%	1.44%[a]	3.03%	2.86%	1.44%[a]	2.24%	3.15%	1.44%

[a] assumed equal to secukinumab

4.1.1.5 Time horizon

Total per-patient costs are presented over a five-year time horizon. The company considered this adequate to reflect any materially important differences in costs between the interventions. The company also presented a number of scenarios with alternative time horizons in response to the ERG's clarification request. The company considered nine years the most relevant time horizon, as

this was most reflective of the predicted 9.09 year mean treatment duration under an assumption of 11% annual discontinuation.

4.1.1.6 Assumptions

The key assumptions in the cost comparison analysis are listed below:

- Upadacitinib is positioned at first and subsequent lines of treatment in the AS pathway (in line with its expected marketing authorisation for AS) (see Sections 2.1 and 4.2.1).
- Secukinumab is the most relevant comparator in bDMARD-naïve patients, whilst ixekizumab and secukinumab are the most relevant comparators in bDMARD-experienced patients (see Sections 2.1 and 4.2.1).
- Equivalent effectiveness between upadacitinib and comparators means that it is appropriate to evaluate upadacitinib in the context of a cost-comparison FTA.
- Equivalent safety profile between intervention and comparators, leading to the exclusion from the comparison of any costs associated with the prevention and treatment of AEs.
- Comparable administration and monitoring costs for bDMARDs and upadacitinib in bDMARD-naïve and -experienced patient population, as no separate analyses are presented by patient population.
- Total per-patient costs are calculated over a five-year time horizon.
- Differential treatment discontinuation rates and dose adjustments due to loss of efficacy or AEs were not considered. Furthermore, patients are assumed to continue on maintenance treatment after the initial response assessment (i.e., discontinuation at initial response assessment for non-responders is not modelled). Therefore, the cost-comparison does not account for the costs of subsequent treatments in initial non-responders or in those that discontinue after initial assessment.

4.1.2 Results

The company presented mean undiscounted annual costs by category of cost for the full population in Table 15 (response to clarification question B6), and for a time horizon of 2, 5, 9, and 10 years in Table 16 (response to clarification question B8).

The results of the company's updated cost comparison analysis, which includes the PAS discount for upadacitinib and uses the list prices for secukinumab and ixekizumab estimated upadacitinib to be [redacted] respectively in the first year of treatment. Over the full five-year time horizon considered in the company's updated base case, the total cost savings using upadacitinib were estimated to be [redacted] versus ixekizumab, and [redacted] versus secukinumab.

The company explored three alternative scenarios regarding the rate of treatment discontinuation to reflect the differences in estimates derived from several alternative sources. See Section 4.2.3 for further details.

In Scenario 1 (6.57% equal annual discontinuation), the five-year cost savings for upadacitinib were increased relative to ixekizumab and secukinumab, to [redacted] respectively. Scenario 2 (11.84% equal annual discontinuation) reduced five-year cost savings to [redacted] versus ixekizumab and secukinumab respectively. In Scenario 3, five-year cost savings for upadacitinib increased to [redacted] versus ixekizumab and secukinumab respectively. However, as only one line of treatment was modelled without capturing health effects, the drug with the highest rate of discontinuation will tend towards greater cost savings over time.

4.2 ERG critique of the company submission

The ERG validated the electronic model by auditing formulae, and cross-checking parameter values and results against the information provided by the company in the CS and response to clarification questions. The ERG detected some inconsistencies in the electronic model submitted by the company at clarification stage. These related to the implementation of the ixekizumab and secukinumab dosing schedules in the model for the purpose of estimating the acquisition costs of these therapies (see Section 4.2.5) and were corrected by the ERG on their preferred base case analysis.

The ERG critique focuses on the following aspects of the cost comparison analysis:

- Population, treatment positioning and relevant comparators;
- Adverse events;
- Treatment adherence and discontinuation;
- Time horizon;
- Acquisition costs;
- Monitoring costs;
- Administration costs.

Following the critique, the ERG proposes an alternative base case analysis, exploring alternative assumptions to those used in the company analysis. The results of the ERG preferred base case are presented in a confidential appendix separate to this report.

The ERG notes that the cost comparison model does not formally model response assessment at the end of the trial period, and therefore, costs are not estimated separately for patients who do not have a response to treatment at this time point, and move to the next line of treatment. Therefore, the differential costs between responders and non-responders to each of the comparators are not captured

in the cost comparison model. This is a limitation of this analysis, but the ERG does not consider it to affect results.

4.2.1 Population, treatment positioning and relevant comparators

The company positions upadacitinib at first or subsequent lines of treatment in the AS pathway (in line with its expected marketing authorisation for this condition), and provides the same cost comparison analysis to support its use in bDMARD-naïve and experienced populations. The company considers secukinumab to be a relevant comparator for bDMARD-naïve and experienced populations, whilst ixekizumab is relevant only for the bDMARD-experienced population.

For the reasons detailed in Section 2.1.2, ERG considers secukinumab to be the relevant comparator for bDMARD-experienced patients, if it upadacitinib is positioned in the treatment pathway for bDMARD-experienced patients as an alternative to IL-17A inhibitors. However, if upadacitinib is considered to constitute an additional line of therapy in AS (i.e., third-line or later), it will displace established clinical management without bDMARDs and cannot be appraised in the context of a cost comparison FTA (see Section 2.2). Adding a line of treatment to the pathway has the potential to change downstream costs and HRQoL outcomes of managing the condition, and needs to be accounted for in a full cost-utility framework.

4.2.2 Adverse events

As detailed in Section 3.3, the ERG is concerned that the safety profile of upadacitinib is potentially different from that of TNF-alpha inhibitors (and IL-17A inhibitors) due to the safety issues identified by regulatory agencies in regards to the use of tofacitinib and JAK inhibitors.[2, 29, 30]

At clarification stage, the ERG requested the inclusion in the cost comparison analysis of costs associated with the prevention, diagnosis, management and treatment of AEs (see clarification question B2). The company chose to not include any AEs costs in their base case analysis, and justified their decision by stating that the safety data submitted in response to clarification questions A3-A5 (critiqued by the ERG in Section 3.3) does not suggest the occurrence of AEs (short or long-term) to be greater in patients treated with upadacitinib compared to patients treated with IL-17A inhibitors. However, the ERG concluded that there is insufficient evidence to establish the equivalence of upadacitinib compared to bDMARDs, especially in terms of long-term safety (see Section 3.3).

The ERG considers that, while the inclusion of AE costs in the cost comparison would have been appropriate, the issue remains that potential differences in the incidence of AEs between upadacitinib and IL-17A inhibitors cannot be fully dealt with within the boundaries of a cost comparison FTA, and

requires a full cost-effectiveness analysis to capture the impact on HRQoL due to the AEs and the consequences of discontinuing treatment (and switching to subsequent lines of therapy).

4.2.3 Treatment adherence and discontinuation

The ERG considers there to be remaining uncertainty regarding the anticipated rate of long-term discontinuation on upadacitinib in clinical practice. Whilst the company have demonstrated that within a trial setting, discontinuation due to AEs was broadly similar on upadacitinib as those for secukinumab and ixekizumab, equivalence in long-term maintenance of the treatment effect is less clear. In order to proceed with a cost comparison analysis, there needs to be high certainty of equivalence in long-term treatment effectiveness. As a first-in-class treatment in this indication, the validity of assuming equal rates of long-term efficacy and treatment withdrawal to established SC biologics based on the data available is highly uncertain, and cannot be corroborated by robust long-term evidence.

The cost comparison framework is unable to capture the consequences of any scenario in which loss of efficacy, or AEs leads to a greater rate of discontinuation on upadacitinib. Furthermore, if MHRA restrictions on the use of tofacitinib are extended to the JAK inhibitor class as a whole, any impact upon discontinuation due to development of risk factors for MACE, VTE, and malignancies would need to be explored in a cost-utility framework to understand the consequences of upadacitinib uptake on health and cost outcomes.

4.2.4 Time horizon

The ERG requested that the cost comparison be updated to allow consideration of alternative time horizons, including a sensitivity analysis with a time horizon equal to estimated mean treatment duration. The company provided scenario analyses in which a 10-year time horizon was used, but considered a 9-year time horizon more appropriate as the estimated mean treatment duration was 9.09 years assuming treatment discontinuation at a constant rate (11% per annum).

Whilst the relative difference in costs between upadacitinib and its comparators remains the same in the additional years modelled in the company's base case analysis, the FTA cost comparison case requires accrued costs to be considered over a time horizon appropriately representing a typical course of treatment. The inclusion of additional monitoring costs for upadacitinib would result in accrual of greater long-term costs to the NHS, and thus a time horizon representing at least the average course of treatment would be required to appropriately capture any important differences. The ERG, therefore, considers that the most relevant time horizon should be reflective of the mean duration of treatment in practice. As this is uncertain, the ERG present base case results for a range of time horizons up to ten years.

However, as previously discussed, the rate of discontinuation anticipated in practice may differ from that observed in the sources used by the company. The ERG presents a scenario analysis exploring the potential impact of the time horizon on the accrual of monitoring costs for upadacitinib and its comparators.

4.2.5 Acquisition costs

The ERG considered that inconsistencies remained in the dosing schedules of ixekizumab and secukinumab after the clarification stage, and updated the company's model submitted at clarification stage to deal with this (this model is referred to henceforth as the ERG revised model). These inconsistencies relate to an assumption on the duration of a trimester expressed in weeks (12 vs. 13.04 weeks in the company and ERG revised model, respectively). The ERG corrected the dosing schedules for both comparators; these are shown in Table 8 alongside those estimated by the company. The ERG preferred base case analysis applies the resource use described for the ERG revised model.

Table 8. Dosing schedules of secukinumab and ixekizumab in the models

Number of doses	Company's model*			ERG revised model*,**		
	1st trimester	2nd trimester	Subsequent trimesters	1st trimester	2nd trimester	Subsequent trimesters
Secukinumab 150 mg	7.00	3.00	3.00	7.08	3.00	3.00
Ixekizumab 80mg	5.00	3.00	3.26	5.26	3.26	3.26

*a year is assumed to correspond to have 365.25 days on average
**on average a month is assumed to correspond to approximately 4.35 weeks, and 3 months approximately 13.04 weeks

Therefore, the ERG revised model estimates that on average, and not accounting for treatment discontinuation, patients would receive:

- 16.08 and 12.00 doses of secukinumab 150mg in the first and subsequent years, respectively.
- 15.04 and 13.04 doses of ixekizumab 80mg in the first and subsequent years, respectively.

4.2.6 Monitoring costs

The ERG was initially unable to validate the unit costs applied by the company to value resource use associated with patient monitoring because the estimates used by the company did not match those in the source reference.[37] The company reported the version of the NHS reference costs[38] used in response to clarification questions. The ERG noted that the magnitude of differences between the two sources are minute and unlikely to affect the results. The unit costs applied in the ERG revised model are presented in Table 11 (Appendix 2); these estimates also include other corrections detailed in Appendix 2. These corrections do not impact the results, as they apply to upadacitinib and comparators equally.

The ERG requested at the clarification stage that further monitoring costs were considered for patients treated with upadacitinib, namely a baseline risk assessment including lipid profiling, blood pressure measurement, body weight measurement, and diabetes tests, and further annual lipid profile monitoring. In response to clarification question B1, the company stated that the only expected difference in monitoring between JAK inhibitors and IL-17A inhibitors is lipid monitoring, and that cardiovascular risk factor assessment is routinely conducted for all patients with AS regardless of treatment type. The company also noted that monitoring protocols may differ between centres treating AS patients receiving JAK inhibitors and IL-17A inhibitors. The company presented a scenario analysis where more intensive monitoring resource use for upadacitinib compared to secukinumab, and ixekizumab in the first three months of treatment was sourced from a protocol provided by a clinical expert to the company (see response to clarification B1, Table 12); this had a negligible impact on results.

4.2.7 Administration costs

The company has selected secukinumab as the most relevant comparator at first line, and both secukinumab and ixekizumab at second line. In the small number of patients initiating secukinumab at first line, it is likely that self-injection training would be provided by the manufacturer free of cost to the NHS. For the comparison in bDMARD-experienced patients, the ERG understands that most patients will have already received training in the use of self-injecting SC administration devices at earlier lines of therapy, and further provision is unlikely to be necessary given the similarity of these devices, and the information provided by the respective manufacturers.

The ERG considers it likely that NHS-funded self-injection training will not be necessary for the comparator therapies, therefore the cost comparison presented by the company may result in an overestimate of the costs associated with secukinumab and ixekizumab. The company provided a scenario analysis in which this cost was omitted; however, the ERG considers this assumption to be most appropriate in the base case analysis.

4.3 ERG preferred base case

The ERG base-case analysis builds on the company's updated base-case analysis submitted at clarification stage; it differs from this by incorporating the following set of assumptions:

1. Monitoring of patients on treatment with upadacitinib requires baseline and annual lipid profile assessment in addition to the monitoring resource use associated with the comparators (see Section 4.2.6);
2. The unit cost of a TB test corresponds to £66.23 (see Section 4.2.6).;

3. Dosing schedules of ixekizumab and secukinumab have been adjusted as described in Section 4.2.5;
4. No administration costs for the treatments under comparison (see Section 4.2.7).

Results of the base case analysis are summarised for the first and subsequent years, in the absence of treatment discontinuation, in the confidential appendix to this report. The appendix also contains results over a number of different time horizons, and at two alternative annual discontinuation rates for all treatments (11% and 6.57%) (see Section 4.1.1.4).

5 ERG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

5.1 Strengths

5.1.1 Clinical evidence

- The clinical trial evidence submitted had sufficiently robust internal validity and its applicability to the NHS was acceptable.
- The evidence provided by the NMA results to compare upadacitinib to secukinumab and ixekizumab in bDMARD-naïve and -experienced populations supports the assumption of equivalent efficacy against these comparators.

5.1.2 Economic evidence

- The electronic model used to inform the cost comparison analysis is simple and transparently presented, and no major errors were identified.
- The company updated the model at the clarification stage to include alternative time horizon durations, which allowed the ERG to explore the impact of varying this parameter.

5.2 Weaknesses and areas of uncertainty

5.2.1 Clinical evidence

- The SmPC for upadacitinib advises it be used with caution in patients at high risk for VTE; estimates suggest around a quarter of AS patients have obesity as a risk factor. MHRA safety warnings of SAEs exist for tofacitinib, another JAK inhibitor. There are therefore grounds to doubt the claim for similarity of safety outcomes of upadacitinib when compared with bDMARDs.
- The company's preferred comparators secukinumab and ixekizumab have very small market shares as first-line therapies. No clear clinical rationale was provided by the company for not

using a TNF-alpha inhibitor as a first-line comparator. The ERG considers the first-line comparator choices to be sub-optimal in terms of market share and representativeness of therapies used in practice.

It is plausible that for most AS patients (though not all), upadacitinib may be used as a new line of therapy. It may sometimes displace the use of a second IL-17A inhibitor or, very rarely, be used as a first-line treatment in needle-phobic patients.

- If upadacitinib were to be mostly used as a new line of therapy then the relevant comparator would be established clinical management without bDMARDs, which was not mentioned in the NICE scope. This would not be a suitable comparator for the FTA process as it would not adequately represent NICE recommended treatments as a whole in terms of cost and effects, and would mean downstream costs would be affected in a way not possible to model in a cost comparison framework.
- The ERG's clinical advisers thought that the option of giving a treatment orally was unlikely to be an important advantage from the perspective of most AS patients, although it is very likely to be beneficial for the very few patients who are needle-phobic.
- Networks of evidence were sparse meaning that relative effect estimates comparing upadacitinib to secukinumab and ixekizumab are uncertain, particularly for the bDMARD-experienced population.
- The assumption of equivalent efficacy and safety (adherence and discontinuation) between upadacitinib and the included comparators beyond the initial response assessment is highly uncertain.

5.2.2 Economic evidence

- The appropriateness of assessing the cost-effectiveness of upadacitinib in the context of a cost comparison FTA relies on the validity of the assumption of equivalent efficacy and safety (adherence and discontinuation) of tofacitinib to at least one relevant comparator.
- The exclusion of the costs associated with AEs from the cost comparison is an important area of uncertainty. If the long-term safety profile of upadacitinib differs to that of the comparators, this exclusion would have uncertain implications for the cost-effectiveness of upadacitinib. Differences in the safety profile could have short-term costs and HRQoL impacts, and could also lead to complications and subsequent events with longer term impacts on health and health system costs (e.g., those associated with MACE and VTE). Differences in the safety profile between interventions could also impact on treatment discontinuation.
- The equivalence of treatment discontinuation rates on upadacitinib with the comparators over the time horizon is highly uncertain, and the potential impact on HRQoL and cost outcomes cannot be quantified in a cost comparison FTA.

- The most relevant time horizon for the cost comparison analysis is uncertain, both the ERG and company's base case results are sensitive to this parameter when confidential PAS prices are considered.
- Costs associated with monitoring patients on treatment with upadacitinib are uncertain and are likely to be higher than what was considered in the cost comparison analysis due to the clinical concerns surrounding the use of JAK inhibitors. This uncertainty in the incremental monitoring costs associated with upadacitinib is further amplified by uncertainties surrounding treatment discontinuation and time horizon duration, as the proportion of patients who would remain on treatment with upadacitinib over time is unknown.

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APPENDICES

APPENDIX 1: NETWORK META-ANALYSES AND DATA INCLUDED

Table 9. Summary of the NMAs conducted in the Upadacitinib FTA

NMA	Population	Assessment Time Point	
		Upadacitinib	Comparator
bDMARD-Naïve			
1*	RCTs with majority bDMARD-naïve patients included.	Week 12	Primary time-point in included RCTs. Except ASSERT study of infliximab, where the 12-week secondary time point used.
2	bDMARD-naïve RCTs only	Week 12	
3	bDMARD-naïve RCTs only	Week 14	
bDMARD-Experienced			
4*	bDMARD-IR RCTs only	Week 12	Week 16
5	bDMARD-IR RCTs only	Week 14	Week 16

*Primary NMAs chosen by the company

Table 10. Studies included in NMAs of each outcome for bDMARD-naïve and bDMARD-experienced populations

Outcomes	bDMARD-naive			bDMARD-experienced	
	Upadacitinib	Ixekizumab	Secukinumab	Upadacitinib	Ixekizumab
ASAS40	SELECT-AXIS 1	COAST-V	MEASURE 1[a] MEASURE 2[a] MEASURE 3[a] MEASURE 4[a] MEASURE 5[a]	SELECT-AXIS 2	COAST-W
BASDAI50†	SELECT-AXIS 1	COAST-V	MEASURE 2[a]	SELECT-AXIS 2	COAST-W
BASDAI CFB‡	SELECT-AXIS 1	COAST-V	MEASURE 1[a] MEASURE 2[a] MEASURE 3[a] MEASURE 4[a] MEASURE 5[a]	SELECT-AXIS 2	COAST-W
BASFI CFB	SELECT-AXIS 1	COAST-V	---	SELECT-AXIS 2	COAST-W

[a] Subgroups of bDMARD-naïve patients from the study were used for the NMA. † The network diagram for BASDAI50 (Appendix D, Figure 70) appears to be incorrect based on the data table for the NMA (Appendix D, Table 73). ‡ The network diagram for BASDAI CFB (Appendix D, Figure 73) appears to be incorrect based on the data table for the NMA (Appendix D, Table 74).
Abbreviations: CFB: Change from baseline

APPENDIX 2: UPDATED MONITORING COSTS

At clarification stage the company corrected the unit cost for the TB test to reflect the use of an interferon gamma release assay (IGRA).According to clinical advice to the ERG the Heaf test is no longer used in clinical practice to detect latent TB. The company replaced the cost of the Heaf test with that of an IGRA test. The company estimated the unit cost of an IGRA by uprating to 2019/20 the sum of the cost of two tests: the QuantiFERON – TB Gold-In Tube (QFT-GIT) and the T-SPOT.TB. These costs were sourced from a recent health technology appraisal (HTA) report.[39] The ERG notes that according to the ERG clinical advisers, both tests are used in clinical practice, but not simultaneously. Therefore, the ERG updated the cost of a TB test to the average cost of QFT-GIT and a T-SPOT.TB in the original source[40] used in the HTA report[39] uprated from 2009/10 to 2019/20 prices.[41]

The company also corrected the cost of a specialist visit to reflect an outpatient visit at a rheumatology service, and updated the cost of a chest X-Ray as per the ERG request (clarification question C6).

Table 11. Monitoring unit costs in the ERG revised model

Monitoring component	Unit cost	Source
Full blood count	£2.56	TA407; [4] Emery et al. (2018); [35] Corbett et al. (2016); [18] NHS Reference Costs 2019/20 [42] (DAPS05 - Total Other Currencies)
Erythrocyte sedimentation rate	£2.56	
Liver function test	£1.20	TA407; [4] Emery et al. (2018); [35] Corbett et al. (2016); [18] NHS Reference Costs 2019/20 [42] (DAPS04 - Total Other Currencies)45
Urea and electrolytes	£1.20	
Chest X-Ray	£32.65	TA718;[16] Emery et al. (2018); [35] Corbett et al. (2016); [18] NHS Reference Costs 2019/20 [42]; (DAPF - Direct access plain film (Currency code).
Tuberculosis test	66.23	Pareek et al. (2013) [40] Average of Quantiferon – TB Gold-in Tube and T-SPOT.TB cost (£56.00) inflated from 2009/10 to 2019/20 prices based on the HCHS/NHSCII pay and prices inflation index in PSSRU Unit Costs of Health and Social Care 2020 [41]
Antinuclear antibody	£7.35	TA407;[4] Emery et al. (2018); [35] Corbett et al. (2016); [18] NHS Reference Costs 2019/20 [42] (DAPS06 - Total Other Currencies)
Double-stranded DNA test	£7.35	
Specialist visit	£149.14	TA407;[4] Emery et al. (2018); [35] Corbett et al. (2016); [18] NHS Reference Costs 2019/20 [42] (WF01A – Rheumatology: Consultant-led non-admitted face-to-face attendance, follow-up.)

DNA, deoxyribonucleic acid; HCHS, hospital & community health services; NHS, National Health Service; NHSCII, NHS cost inflation index; PSSRU, Personal Social Services Research Unit.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Upadacitinib for treating active ankylosing spondylitis [ID3848]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG 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 09 May 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 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Safety concerns

General comment Safety concerns for JAK inhibitors are based on the ORAL SURVEILLANCE study, which was conducted in a rheumatoid arthritis (RA) patient population, assessing tofacitinib versus TNF inhibitors.[1,2] Based on this evidence, the FDA and MHRA have acted cautiously and ensured that precautions are taken against a potential JAK inhibitor class safety effect. • No randomised controlled trials in RA populations similar to that studied in ORAL SURVEILLANCE are available with the other JAK inhibitors to evaluate these safety concerns. Further there are no head-to-head studies comparing JAK inhibitors. The JAK inhibitors have different levels of specificity for the JAK enzymes: JAK1, JAK2, JAK3 and TYK2.[4] While tofacitinib and baricitinib have a broad range of activity, upadacitinib has been shown to be more selective using *in vitro* kinase assays.[4] In consideration of this and in the absence of direct head-to-head studies, the benefit-risk profile of one JAK inhibitor should not be extrapolated to the entire JAK inhibitor class • Based on studies of upadacitinib in patients with RA in which adalimumab is included as an active comparator, the rates of MACE, malignancy, VTE and mortality were similar between upadacitinib 15mg and adalimumab treatment arms • AbbVie closely monitors the safety of upadacitinib through post approval pharmacovigilance and long-term follow-up of patients from phase 3 clinical studies across multiple indications. Data from these long-term studies are regularly published and do not indicate any potential signal for elevated risk of VTE, MACE or malignancies (excluding NMSC) with upadacitinib compared with adalimumab or methotrexate. • Additionally, it should be noted that the AS population is not the RA population. Clinicians comment that in terms of rheumatology, on average, AS patients are younger and tend to have fewer comorbidities and risk factors compared to RA patient. **Long-term and AS safety data** • Extensive safety data has been gathered for upadacitinib, both generally across indications and specifically in the AS indication. The safety profile of upadacitinib with up to 4.5 years of exposure in patients (RA, PsA and AS) remained unchanged over long-term treatment compared with previous analyses.[5] The safety profile of upadacitinib 15 mg in patients with PsA and AS was consistent with that observed in RA, with no new safety signals observed.[6,7]	**ERG response** Not a factual inaccuracy. No amendment suggested.

• After up to 2 years of follow-up, there were no serious infections, non-melanoma skin cancer (NMSC), MACEs or VTEs reported in the SELECT-AXIS 1 trial.[8] In SELECT-AXIS 1, the proportion of patients with AEs was generally similar in the upadacitinib and placebo groups. • No serious infections, malignancies, anaemia, lymphopenia, herpes zoster, renal dysfunction, adjudicated major adverse cardiovascular events, venous thromboembolic events, or deaths were reported, and haemoglobin levels remained consistent throughout the first 14 weeks of the study. No new safety findings, serious infections, active tuberculosis, adjudicated MACE, lymphoma, non-melanoma skin cancer, renal dysfunction, or gastrointestinal perforations were observed over 2 years. Based on this evidence, upadacitinib can be considered to align with the safety profiles previously observed with IL-17A inhibitors.			
Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Section 2.1.1 Page 11 The ERG report states: "This is because of an MHRA safety warning about another JAK inhibitor, tofacitinib (see Section 3.3), and concerns that this safety issue may extend to the JAK treatment class as a whole." This statement is imprecise.	This should be amended to: "This is because of an MHRA safety warning about another JAK inhibitor, tofacitinib (see Section 3.3), and there are concerns that this safety issue may extend to the JAK treatment class as a whole."	The statement currently implies that the MHRA safety warning included concerns that this safety issue extended to the JAK inhibitor class. However, this was not included in the safety warning.	Thank you, this wording has been updated.

Section 3.3.1 Page 26-27 The ERG report states: "Moreover, the ERG notes that a class safety effect has already been observed insomuch that upadacitinib, filgotinib, baricitinib and tofacitinib all have special warnings and precautions for use with their SmPCs stating that they should be used with caution in patients with risk factors for deep venous thrombosis and pulmonary embolism." This statement is misleading.	The statement requires clarification	The ERG is correct to note the special warning and precaution for use as a result of a potential class safety effect. However, no evidence of this safety effect has been observed for upadacitinib. The observation made by the ERG (upadacitinib, filgotinib, baricitinib and tofacitinib all have special warnings and precautions for use within their SmPCs) is not the observation of a class effect – it is the observation of a precaution against a class effect.	Thank you, the text has been updated to the following: "Moreover, the ERG notes that there is a potential class safety effect; upadacitinib, filgotinib, baricitinib and tofacitinib all have special warnings and precautions for use, with their SmPCs stating that they should be used with caution in patients with risk factors for deep venous thrombosis and pulmonary embolism."

Section 1.1 Page 8 The ERG report states: "estimates suggest around a quarter of ankylosing spondylitis (AS) patients have obesity as a risk factor" Section 5.2.1 Page 37 The ERG report states: "estimates suggest around a quarter of AS patients have obesity as a risk factor" No reference is provided for this statement, but the study cited in the main body of the report (reference 3, cited Section 2.1.1) provides the proportion of patients who are obese. However, this study does not link obesity as a risk factor for AS.	Assuming no evidence linking obesity as a risk factor for AS has been identified, this should be amended to: "estimates suggest that a quarter of patients with ankylosing spondylosis (AS) are classed as obese, which is a risk factor for VTE.[3]"	No reference is provided for this statement, but the study cited in the main body of the report (reference 3, cited Section 2.1.1) provides the proportion of patients who are obese. However, this study does not link obesity as a risk factor for AS. No other link between obesity and AS has been identified in the document.	The text has been amended to clarify that the risk relates to VTE.

Issue 2 Positioning

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
General comment Upadacitinib has been submitted for its use in the population in second line treatments where TNF- alpha inhibitors do not control the condition and different mode of action is needed. Additionally, upadacitinib is submitted for the population where TNF- alpha inhibitors are considered unsuitable. AbbVie has observed that upadacitinib positioning is not clear through the document and there is a need to reinforce the messages related to scope of this appraisal. The scope provides a framework for the appraisal and defines the issues of interest (for example, population and comparators) as clearly as possible. It also sets the boundaries for the work undertaken by those producing reports for the appraisal committee, including the independent academic group and AbbVie. Abbvie understands there was a change in positioning of Upadacitinib for the population in which TNF- alpha inhibitors would be considered unsuitable or where they do not control the condition well enough, compared to secukinumab and ixekizumab. This was communicated following the scrutiny meeting held in February 2022. It is our understanding that the positioning formed the basis of recommendation to proceed as a FTA (cost-comparison) route for this appraisal.			Not a factual inaccuracy. The change in positioning following the scrutiny meeting (February 2022) has not been communicated to the ERG and was not known at the time of writing the ERG report. Amendments based upon these changes have not been made to the ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2 Page 8 The ERG report states: “The company stated that the most relevant comparators for upadacitinib would be Interleukin-17A (IL-17A) inhibitors (secukinumab and ixekizumab) in either the bDMARD-naïve or -experienced populations.” This is imprecise. The company considers that IL-17A inhibitors are the most relevant comparators, specifically secukinumab in the bDMARD-naïve population and both secukinumab and ixekizumab in the bDMARD-experienced population, in line with current NICE recommendations and market share.	This statement should be updated to read: “The company stated that the most relevant comparators for upadacitinib would be Interleukin-17A (IL-17A) inhibitors: secukinumab in bDMARD-naïve patients; secukinumab and ixekizumab in the bDMARD-experienced population.	The current wording is imprecise. Ixekizumab is not considered the most relevant comparator in the bDMARD-naïve setting, in line with guidance from NICE TA718.[11]	Not a factual inaccuracy. The ERG is quoting from the company response to clarification question A4.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2 Page 8 The ERG report states: “The ERG’s clinical advisers considered secukinumab to have a very small market share (around 5%) as a first-line (i.e. bDMARD-naïve) therapy and ixekizumab an even smaller share.” AbbVie agrees that IL-17 inhibitor usage is small in the bDMARD-naïve setting. However, the ERG statement does not acknowledge the decision making process that occurs in clinical practice, which would position upadacitinib as an alternative to IL-17 inhibitor usage rather than TNFi.	This statement should be amended for clarity. Please refer to general comment under positioning section above.	As noted in the Company Submission (Section B.1.3.3, page 15), in most bDMARD- naïve patients, clinicians would prescribe a TNFi over secukinumab, unless there is a clinical need to use an IL-17 inhibitor over a TNFi. This may be patients with contraindications to TNFi use, but the market share for secukinumab indicates usage beyond just contraindications. Given the established role for TNFi in the AS treatment pathway and the available clinical evidence, upadacitinib is unlikely to displace TNFi use and is likely to be considered as an alternative to secukinumab in bDMARD-naïve patients (i.e. where there is a clinical reason to prefer an alternative TNFi usage). Hence, a comparison with IL-17 inhibitors is more relevant to UK clinical practice.	Not a factual inaccuracy.

Section 1.2 Page 8 The ERG report states: “No clear clinical rationale was provided by the company for not using a tumour necrosis factor-alpha (TNF-alpha) inhibitor as a first-line comparator.” Section 5.2.1 Page 38 The ERG report states: “No clear clinical rationale was provided by the company for not using a TNF-alpha inhibitor as a first-line comparator.” This statement is not accurate.	This statement should be removed. Please refer to general comment under positioning section above.	The rationale for not including a TNFi comparison was provided in the Company Submission. This was reiterated in response to ERG clarification questions. Hence, this statement is not accurate.	The ERG maintains there was uncertainty around the positioning of updacitinib and whether it was suggested that upadacitinib would be used in biological naïve population who were not TNF contra-indicated. In response to clarification on this, the following was provided: “Secukinumab is recommended by NICE, within its marketing authorization, as an option for treating active AS in adults whose disease has responded inadequately to conventional therapy (NSAIDs) or TNF-alpha inhibitors. Internal market research, included in our submission, indicates that secukinumab continues to hold a significant market share within the biologic naïve population, which would indicate use outside of just TNF contra-indicated patients. Clinician

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
			feedback has confirmed that the most relevant comparator for upadacitinib would be IL-17s (both secukinumab and ixekizumab) in either the biologic naïve or experienced populations. As such, this is the basis of our clinical and cost comparison in biologic naïve patients." As such the ERG maintain that there was no *clear* rationale for not using a tumour necrosis factor-alpha (TNF-alpha) inhibitor as a first-line comparator, and the statement remains.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2 Page 9 The ERG report states: "If used as a new line of therapy (i.e. the last line of therapy), then the relevant comparator would be established clinical management without bDMARDs."	This statement should be amended.	The use of upadacitinib in the last line of therapy was not discussed within the decision problem issued by NICE. Likewise, established clinical management without biologics was not identified as a comparator during the consultation on the draft scope. Therefore, it is unclear how relevant this would be to the appraisal of upadacitinib and why NICE would choose to restrict usage to a third-line setting by emphasising a comparator that is not currently within the scope of this appraisal.	Not a factual inaccuracy.
Section 2.1.2 Page 12 The ERG report states: "As having a significant market share is one of the FTA process criteria to establish the relevance of a comparator, the ERG considers secukinumab to be the relevant comparator for bDMARD-experienced patients." However, this does not reflect the available clinical evidence for secukinumab in bDMARD-experienced patients.	This statement should be amended: "As having a significant market share is one of the FTA process criteria to establish the relevance of a comparator, the ERG considers secukinumab to be the relevant comparator for bDMARD-experienced patients, although it is acknowledged that secukinumab clinical data for this population is limited."	While the MEASURE 1-5 trials[12-15] for secukinumab enrolled a mixed population, very few bDMARD-experienced patients were enrolled and limited data for this subgroup were reported.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2 Page 14 The ERG report states: “If upadacitinib were to be mostly used as a new line of therapy then the relevant comparator would be established clinical management without biologics, which was not mentioned in the NICE scope. In addition, this would not be a suitable comparator for the FTA process as it would not adequately represent the NICE recommended treatments as a whole in terms of cost and effects.”	This statement should be amended.	Use of upadacitinib after prior TNFi and IL-17A inhibitor use was not discussed within the decision problem issued by NICE. Further, established clinical management without biologics was not identified as a comparator during the consultation on the draft scope, despite inclusion of a question for consultation addressing this issue. As such, it is unclear how relevant this would be to the appraisal of upadacitinib. Further, this does not align with current clinical practice as outlined in the ERG report, where patients typically receive two lines of treatment. As outlined above, the ERG clinical experts emphasised that variation in upadacitinib use would be expected, depending on the extent of concerns about the risk of serious adverse events (SAEs) and on how soon the use of a treatment with a new mode of action was deemed appropriate. As such, it is unclear why NICE may choose to restrict future usage to a third-line setting by emphasising a comparator that is not currently within the scope of this appraisal.	Not a factual inaccuracy. The ERG maintains that there was uncertainty around the positioning of upadacitinib in the company submission and response to clarification. As this is discussion of that uncertainty and the consequences of an alternative positioning for FTA process, the statement remains in the ERG report.

Issue 3 Adherence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.6 Page 10 The ERG report states: "Furthermore, loss of efficacy over time due to adherence issues or other uncharacterised reasons may lead to differences in long-term rates of discontinuation" There is no evidence to support this statement for upadacitinib.	This statement should be amended for accuracy. For example "Although there is currently no evidence, loss of efficacy over time due to adherence issues or other uncharacterised reasons may lead to differences in long-term rates of discontinuation"	Evidence for upadacitinib indicates sustained benefit in AS through to 64 weeks.[9] Further, evidence in other indications shows that upadacitinib is safe and efficacious. Thus, there is no evidence to support a particular loss in adherence and/or efficacy for upadacitinib.	This is a discussion of an area of uncertainty, in which there are limited long-term data, the sentence has been amended to make it clearer that this is a discussion of an area of uncertainty: "Furthermore, loss of efficacy over time due to *potential* adherence issues or other uncharacterised reasons may lead to differences in long-term rates of discontinuation."

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.1.3 Page 14 The ERG report states: "However, clinical advice to the ERG was that adherence and compliance with a twice-daily tablet may possibly be problematic for some patients." In addition to the relevance of a twice-daily regimen to upadacitinib (see Issue 7), there is no evidence to support this suggestion.	This statement should be deleted or amended for clarity.	As noted in the ERG report, available clinical trial evidence supports high levels of adherence for upadacitinib. During SELECT-AXIS 1 and 2, compliance was 97.9% and 97.4% respectively. Further, evidence for upadacitinib indicates sustained benefit in AS through to 64 weeks.[9] Further, evidence in other indications shows that upadacitinib is safe and efficacious. Thus, there is no evidence to support a particular loss in adherence and/or efficacy for upadacitinib. Additionally, upadacitinib is not administered a twice-daily tablet; it is a once daily tablet.	Thank you, this has been amended - although comments regarding the adherence to taking tablets stand for a once daily medication.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.1.3 Page 14 The ERG report states: "older patients may have polypharmacy issues (i.e. they take too many tablets to remember to take them all)"	This statement should be deleted.	Polypharmacy refers to the use of multiple medications and/or the administration of more medications than are clinically indicated.[12] Polypharmacy is of greater concern in elderly patients and may result in increased risk of adverse drug reactions or drug-drug interactions. While this is an important prescribing issue; AS patients are generally healthier and have less comorbidities; therefore, are more likely to be on less medication.	Not a factual inaccuracy. This statement has relevance to medication compliance of older patients who may take upadacitinib in the NHS population.
Section 2.1.3 Page 14 The ERG report states: "The ERG also notes that due to the biological half-life of upadacitinib, missed doses, treatment interruptions, and other issues leading to reduced adherence…." Treatment interruptions are managed directly by clinicians in response to adverse events. Hence, treatment interruptions are not adherence issues.	Treatment interruptions should be removed from this sentence.	Treatment interruptions are important tools for clinicians to manage adverse events. The SmPC for upadacitinib includes specific guidelines on when treatment interruptions are required. Classing treatment interruptions as an adherence issue leading to loss of clinical effectiveness could potentially misinform patients and reduce compliance with clinician advice.	Thank you for highlighting this, the text has been amended to remove treatment interruptions from the sentence.

Issue 4 Clinical trial design and outcomes

Issue 5 Indirect treatment comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.4.1 Page 19 The ERG report states: "Previous appraisals in AS have conducted NMAs to evaluate the relative efficacy and safety of TNF-alpha inhibitors (TA383), secukinumab (TA407) and ixekizumab (TA718) compared to other available bDMARDs." However, no previous appraisal has assessed safety in an NMA.	The statement should be amended as follows: "Previous appraisals in AS have conducted NMAs to evaluate the relative efficacy of TNF-alpha inhibitors (TA383), secukinumab (TA407) and ixekizumab (TA718) compared to other available bDMARDs."	As noted in Table 3 of the ERG report, no previous HTA has included an ITC for safety. It is acknowledged that the company submission for TA718 (ixekizumab)[11] mentioned an ITC for safety outcomes; however, no outcomes are presented as noted in the ERG report for this HTA.	Thank you, this text has been, amended.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.4.2 Page 22 The ERG report states: “The company’s clinical advisors expect the comparison between the efficacy of upadacitinib and secukinumab to be similar in the bDMARD-naïve and bDMARD-experienced populations. The ERG’s clinical advisors had reservations about this claim, as treatment benefits tend to fall after a patient has had experience with a bDMARD, but it is naïve to assume that the decrease in treatment effect would be similar in upadacitinib (a JAK inhibitor) and secukinumab (as IL-17A inhibitor) as both drugs have different mechanisms of action.” This is a misunderstanding of the statement in the company submission	This statement should be amended. “	The conclusion from the NMA is that there were no significant differences between upadacitinib and IL-17A inhibitors across endpoints, across timepoints, across populations and across methodologies. In that context, a comparison of upadacitinib and secukinumab in bDMARD-experienced populations may output different values, but the it is anticipated that the conclusions from the NMA would remain unchanged (i.e. there is similar efficacy between upadacitinib and IL-17A inhibitors).	This sentence has been amended to clarify the point of the clinical advice to the ERG: The ERG’s clinical advisors had reservations about this claim, as treatment benefits tend to fall after a patient has had experience with a bDMARD, but it is naïve to assume that the effectiveness would decline similarly for different classes of drugs as JAK inhibitors and IL-17A inhibitors have different mechanisms of action.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.4.2 Page 22 The ERG report states: "…as treatment benefits tend to fall after a patient has had experience with a bDMARD…." It is acknowledged that absolute outcomes may fall slightly,but noted that comparative outcomes for upadacitinib are comparable or slightly increased for bDMARD-experienced versus bDMARD-naïve.	This sentence should be clarified.	No drop in comparative effectiveness benefit was observed for upadacitinib following experience with a bDMARD. During SELECT-AXIS 1, ASAS40 was 51.6% for upadacitinib and 25.5% for placebo, providing a response rate difference of 26.1%. During SELECT-AXIS 2, ASAS40 was 44.5% for upadacitinib and 18.2% for placebo, providing a response rate difference of 26.4%. Comparable or slightly increased relative outcomes were observed for ASDAS (CRP), BASDAI50, BASFI, BASMI, MASES, ASAS health index.	The sentence has been amended to clarify the clinical advice to the ERG: The ERG's clinical advisors had reservations about this claim, as treatment benefits tend to fall after a patient has had experience with a bDMARD, but it is naïve to assume that the effectiveness would decline similarly for different classes of drugs as JAK inhibitors and IL-17A inhibitors have different mechanisms of action.

Issue 6 Cost comparison analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4 page 9 The ERG report states: “Costs relating to monitoring may have been underestimated for upadacitinib” Section 5.2.2 page 39 The ERG report states: “Costs associated with monitoring patients on treatment with upadacitinib are uncertain and are likely to be higher than what was considered in the cost comparison analysis due to the clinical concerns surrounding the use of JAK inhibitors.” Underestimation of monitoring costs is not fully discussed later in the report. Further, a scenario was provided in response to clarification questions wherein intensive monitoring resource use was assumed based on a protocol provided a clinical expert. This had minimal impact on the cost comparison analysis. As a result, it is unclear where the underestimation may lie.	These statements should be removed. Alternatively, additional discussion around where monitoring may be underestimated should be provided.	As no details for this underestimation are provided, it is difficult to assess the plausibility of the suggestion. However, a scenario was provided in response to clarification questions wherein intensive monitoring resource use was assumed based on a protocol provided a clinical expert. This had minimal impact on the cost comparison analysis.	Not a factual inaccuracy. The ERG report directly cites clinical concerns regarding the safety of JAK inhibitors as a reason that monitoring costs may be higher in practice. This will depend on how risk averse individual clinicians are. The sentence in section 5.2.2 has been amended to: “Costs associated with monitoring patients on treatment with upadacitinib are uncertain and *may* be higher than what was considered in the cost comparison analysis due to the clinical concerns surrounding the use of JAK inhibitors.”

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4 page 9 The ERG report states: “costs relating to the treatment of adverse events (AEs) were not included. The magnitude of these costs and their relevance to upadacitinib and the comparators represents a source of uncertainty”	This statement should be amended	To have a large impact on a cost comparison analysis, an adverse event would need to be high frequency or have a large cost or quality of life impact. Impactful adverse events were rarely observed during SELECT-AXIS 1 and SELECT-AXIS 2. Further, impactful events were rare even in the tofacitinib study ORAL SURVEILLANCE (A3921133), which precipitated the safety warnings. For example, MACE events were significantly increased in patients receiving tofacitinib compared with TNF inhibitors, but were observed in 3.4% of patients over a four year period (compared with 2.5% in patients receiving TNFi), which is equivalent to 0.91 patients with events per 100 patient-years.[1,2] As such, even modelling this highly impactful adverse event would have limited impact on cost accrual.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.2 Page 34 The ERG report states: “while the inclusion of AE costs in the cost comparison would have been appropriate, the issue remains that potential differences in the incidence of AEs between upadacitinib and IL-17A inhibitors cannot be fully dealt with within the boundaries of a cost comparison FTA, and requires a full cost-effectiveness analysis to capture the impact on HRQoL due to the AEs and the consequences of discontinuing treatment (and switching to subsequent lines of therapy).”	This statement should be amended.	As noted under Issue 1, the observed evidence for upadacitinib does not suggest increased adverse events versus secukinumab and ixekizumab. Modelling this observed data may lead to minor changes in QALY accrual, but would not support decision making.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.1.5 Page 30-31 The ERG report states: “The company considered nine years the most relevant time horizon, as this was most reflective of the predicted 9.09 year mean treatment duration under an assumption of 11% annual discontinuation.” Section 4.3.4 Page 35 The ERG report states: “The company provided scenario analyses in which a 10-year time horizon was used, but considered a 9-year time horizon more appropriate as the estimated mean treatment duration was 9.09 years assuming treatment discontinuation at a constant rate” This is inaccurate.	This statement should be amended.	The company did not state that nine years was the most relevant time horizon. The company provided this time horizon as a relevant scenario for the ERG’s request.	Text has been amended to read: ‘The company also considered a nine-year time horizon, reflecting the predicted 9.09 year mean treatment duration…”

Issue 7 Benefits of oral treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.1.3 Page 14 The ERG report states: “As such these comparator treatments are thought unlikely to be much more burdensome to patients than a twice-daily oral option” The ERG report also states: “However, clinical advice to the ERG was that adherence and compliance with a twice-daily tablet may possibly be problematic for some patients.” The relevance to upadacitinib once-daily is unclear. Alternatively, this may be an inaccuracy, as upadacitinib is administered once daily.	The relevance of twice-daily oral options to upadacitinib should be made clear. Alternatively, the text should be corrected.	Upadacitinib is a once-daily oral therapy. It is unclear why a comparison between twice-daily treatment and injectable therapies would be relevant to appraisal of upadacitinib. A survey of patients with axial spondyloarthritis found that 51.4% would prefer an oral treatment, stating that the main advantages were the easy administration (58.3%), no need for a special skill (33.3%) and no requirement for refrigeration (16.7%).[10] As such, the ERG statement does not reflect the patient experience.	Thank you, this has been amended - although comments regarding the adherence to taking tablets stand for a once daily medication. The text now reads: “As such these comparator treatments are thought unlikely to be much more burdensome to patients than a once -daily oral option” “However, clinical advice to the ERG was that adherence and compliance with a once-daily tablet may possibly be problematic for some patients.”

Issue 8 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.5 Page 9-10 The ERG report states: "Due to the short biological half-life of upadacitinib relative to bDMARDs (hours vs. weeks), adherence issues may present a greater issue with regards to maintenance of response, adherence issues leading to missed doses of upadacitinib due to may have a greater impact upon continuing efficacy, with potentially important implications for maintenance of response."	This should be amended to (amendment in red): "Due to the short biological half-life of upadacitinib relative to bDMARDs (hours vs. weeks), adherence issues may present a greater issue with regards to maintenance of response. Adherence issues leading to missed doses of upadacitinib 1may have a greater impact upon continuing efficacy, with potentially important implications for maintenance of response."	Grammar error	Amended.
Section 2 Page 11 The ERG report states: "…because this was unclear from the CS The company stated that from…."	This should be amended to (amendment in red): "…because this was unclear from the CS. The company stated that from…."	Grammar error	Amended.
Section 3.2.4.1 Page 22 The ERG report states: "In the original CS, the company did not consider an NMA assuming class effects for IL-17A inhibitors" This is a potential typographical error	If this is an error, this should be amended to: "In the original CS, the company did not consider an NMA assuming class effects for JAK inhibitors"	It is correct that the submission did not consider a class effect for IL-17A inhibitors or JAK inhibitors. However, in the context, it is presumed that the ERG intended to discuss a class effect for JAK inhibitors.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.1 Page 33 The ERG report states: “ERG considers secukinumab to be the relevant comparator for bDMARD-experienced patients, if it upadacitinib is positioned in the treatment pathway for bDMARD-experienced patients as an alternative to IL-17A inhibitors.” This a typographical error.	This should be amended to (amendment in red): “ERG considers secukinumab to be the relevant comparator for bDMARD-experienced patients, if ~~it~~ upadacitinib is positioned in the treatment pathway for bDMARD-experienced patients as an alternative to IL-17A inhibitors.	Additional word	Amended
Section 5.2.1 Page 37 The ERG report states: “The SmPC for upadacitinib advises it be used with caution in patients at high risk for VTE” There is a missing word	This should be amended to (amendment in red): “The SmPC for upadacitinib advises it should be used with caution in patients at high risk for VTE”	Missing word	Amended

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4 Page 28 The ERG report states: “The ERG also highlights throughout the subsequent subsections, features of the cost comparison that may be affected by uncertainty surrounding the validity of assuming equivalent efficacy and safety of tofacitinib to at least one relevant comparator.” Section 5.2.2 Page 38 The ERG report states: “The appropriateness of assessing the cost-effectiveness of upadacitinib in the context of a cost comparison FTA relies on the validity of the assumption of equivalent efficacy and safety (adherence and discontinuation) of tofacitinib to at least one relevant comparator.” This appraisal is assessing upadacitinib	This should be amended to (amendment in red): “The ERG also highlights throughout the subsequent subsections, features of the cost comparison that may be affected by uncertainty surrounding the validity of assuming equivalent efficacy and safety of upadacitinib to at least one relevant comparator.” “The appropriateness of assessing the cost-effectiveness of upadacitinib in the context of a cost comparison FTA relies on the validity of the assumption of equivalent efficacy and safety (adherence and discontinuation) of upadacitinib to at least one relevant comparator.”	Wrong drug name	Amended
Appendix 2 Page 43 Table 11 The NHS reference cost citation should be reference 38.	The NHS reference cost citation should be reference 38.	Incorrect citation.	Thank you for this. We have updated the references in Table 11.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.1.3 Page 13 The ERG report states: “The CS (page 92) stated that there is a high unmet treatment need in AS for treatment options offering an alternative mechanism of action and mode of administration.”	Amend to reflect the correct page number, page 93 of the CS	The text that is referred to is not on page 92 of the CS as stated. Page 93 of the CS states “There is a high unmet treatment need in AS for more treatment options offering an alternative mechanism of action and mode of administration to currently available IL-17A inhibitors"	Amended
Section 3.2.3 Page 18 The ERG report states: “Efficacy results for key primary and secondary end-points are reported for SELECT-AXIS 1 in section B.3.6.1.6 of the CS”	Amend text to reflect correct location of key secondary end-point results	Efficacy results for key primary end-points are reported for SELECT-AXIS 1 in section B.3.6.1.6 of the CS. However, key secondary end-points are reported in section B.3.6.1.7.	Amended
Section 4.1.1.2 Page 29 line The ERG report states: “Personal Social Services Research Unit, (PSSRU) 2019”	Amend text to correct the year “2019” to “2020” as per the CS	Typographical error	Amended

Confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Section 2.1.3 Page 14 Line 14	The report states that: “Compliance with upadacitinib 15mg was reported in the CSR for	“Compliance with upadacitinib 15mg was reported in the CSR for	Amended

	SELECT-AXIS 1 as [redacted] at 14 weeks follow-up," This value should be marked AIC and not CIC.	SELECT-AXIS 1 as [redacted] at 14 weeks follow-up,"	
Section 3.3.2 Page 27 Lines 4-10	The report states that: "Discontinuation of upadacitinib 15mg due to AEs is reported for the SELECT-AXIS 1 study, as [redacted] at 14 weeks follow-up and [redacted] at 104 weeks follow-up (Tables 4 and 6 of the CSR). This is consistent with that demonstrated in clinical trials of upadacitinib for other indications including psoriatic arthritis and RA.[31] For SELECT-AXIS 2 data are only reported at 14 weeks follow-up as [redacted] (Table 1 of the CSR). Discontinuation due to lack of efficacy is only reported for the SELECT-AXIS 1 study at 104 weeks follow-up ([redacted] (Table 6 of CSR) and SELECT-AXIS 2 study at 14 weeks follow-up ([redacted] (Table 1 of CSR)." These values should be marked AIC and not CIC.	Discontinuation of upadacitinib 15mg due to AEs is reported for the SELECT-AXIS 1 study, as [redacted] at 14 weeks follow-up and [redacted] at 104 weeks follow-up (Tables 4 and 6 of the CSR). This is consistent with that demonstrated in clinical trials of upadacitinib for other indications including psoriatic arthritis and RA.[31] For SELECT-AXIS 2 data are only reported at 14 weeks follow-up as [redacted] (Table 1 of the CSR). Discontinuation due to lack of efficacy is only reported for the SELECT-AXIS 1 study at 104 weeks follow-up ([redacted] (Table 6 of CSR) and SELECT-AXIS 2 study at 14 weeks follow-up ([redacted] (Table 1 of CSR).	Amended
Section 4.1.1 Page 29 Table 6	The drug acquisition unit cost for upadacitinib (row 3, column 2) reads: Rinvoq (15mg, pack of 28): £805.56 (list price), [redacted] [redacted] (PAS price) This is missing the CIC marking for the pack price of upadacitinib including the PAS, which is confidential.	Rinvoq (15mg, pack of 28): £805.56 (list price), [redacted] [redacted] (PAS price)	Amended

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