Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

CONFIDENTIAL UNTIL PUBLISHED

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.)

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright statement

Copyright belongs to the University of York

Copyright is retained by AbbVie for tables and figures copied and/or adapted from the company submission and other submitted company documents.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

Table of Contents

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

Table of Tables

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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,

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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]

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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).

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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).

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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).;

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.

6 REFERENCES

1. AbbVie / HEOR Ltd. Advisory board report: upadacitinib for the treatment of active ankylosing spondylitis *Data on file* 2021.
2. U.S. Food and Drug Administration. *Janus Kinase (JAK) inhibitors: Drug safety communication - FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death*. 2021. Available from: https://www.fda.gov/safety/medical-product-safety-information/janus-kinase-jak-inhibitors-drug-safety-communication-fda-requires-warnings-about-increased-risk [accessed 17 December 2021]
3. Prior-Español A, Sánchez-Piedra C, Campos J, Manero FJ, Pérez-García C, Bohórquez C, et al. Clinical factors associated with discontinuation of ts/bDMARDs in rheumatic patients from the BIOBADASER III registry. *Scientific reports* 2021;**11**:11091.
4. National Institute for Health and Care Excellence. *Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors. Technology appraisal guidance [TA407]*. London: NICE; 2016.
5. de Winter JJ, van Mens LJ, van der Heijde D, Landewé R, Baeten DL. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. *Arthritis research & therapy* 2016;**18**:196-.
6. National Institute for Health and Care Excellence. *Single technology appraisal: secukinumab for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy [ID719] Committee Papers*. London: NICE; 2016.
7. Roche D, Badard M, Boyer L, Lafforgue P, Pham T. *Systematic literature review and network meta-analysis comparing incidence of uveitis and IBD in axial spondyloarthritis patients treated with anti-TNF versus anti-IL17A in placebo controlled randomized trials [abstract]*. 2019. Available from: https://acrabstracts.org/abstract/systematic-literature-review-and-network-meta-analysis-comparing-incidence-of-uveitis-and-ibd-in-axial-spondyloarthritis-patients-treated-with-anti-tnf-versus-anti-il17a-in-placebo-controlled-randomiz/ [accessed January 20 2022]
8. Olivera PA, Lasa JS, Bonovas S, Danese S, Peyrin-Biroulet L. Safety of janus kinase inhibitors in patients with inflammatory bowel diseases or other immune-mediated diseases: A systematic review and meta-analysis. *Gastroenterology* 2020;**158**:1554-73.e12.
9. Deodhar A, Mease PJ, McInnes IB, Baraliakos X, Reich K, Blauvelt A, et al. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. *Arthritis Research & Therapy* 2019;**21**:111.
10. National Institute for Health and Care Excellence. *Single technology appraisal: user guide for company evidence submission template*. London: NICE; 2017.
11. Sieper J, Deodhar A, Marzo-Ortega H, Aelion JA, Blanco R, Jui-Cheng T, et al. Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: results from the MEASURE 2 Study. *Ann Rheum Dis* 2017;**76**:571-92.

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

12. Braun J, Baraliakos X, Deodhar A, Baeten D, Sieper J, Emery P, et al. Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. *Ann Rheum Dis* 2017;**76**:1070-7.
13. Dougados M, Wei JC, Landewé R, Sieper J, Baraliakos X, Van den Bosch F, et al. Efficacy and safety of ixekizumab through 52 weeks in two phase 3, randomised, controlled clinical trials in patients with active radiographic axial spondyloarthritis (COAST-V and COAST-W). *Ann Rheum Dis* 2020;**79**:176-85.
14. European Medicines Agency. *RINVOQ summary of product characteristics*. Amsterdam: EMA; 2021.
15. Van den Bosch F, Poddubnyy D, Stigler J, Ostor A, D'Angelo S, Navarro-Compán V, et al. POS0923 influence of baseline demographics on improvements in disease activity measures in patients with ankylosing spondylitis receiving upadacitinib: A post hoc subgroup analysis of select-axis 1. *Ann Rheum Dis* 2021;**80**:722-3.
16. National Institute for Health and Care Excellence. *Ixekizumab for treating axial spondyloarthritis. Technology appraisal guidance [TA718]*. London: NICE; 2021.
17. Lorenzin M, Ometto F, Ortolan A, Felicetti M, Favero M, Doria A, et al. An update on serum biomarkers to assess axial spondyloarthritis and to guide treatment decision. *Therapeutic Advances in Musculoskeletal Disease* 2020;**12**.
18. Corbett M, Soares M, Jhuti G, Rice S, Spackman E, Sideris E, et al. Tumour necrosis factor-α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. *Health Technol Assess* 2016;**20**:1-334, v-vi.
19. Glintborg B, Østergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. *Ann Rheum Dis* 2010;**69**:2002.
20. Vastesaeger N, van der Heijde D, Inman RD, Wang Y, Deodhar A, Hsu B, et al. Predicting the outcome of ankylosing spondylitis therapy. *Ann Rheum Dis* 2011;**70**:973.
21. Schramm-Luc A, Schramm J, Siedliński M, Guzik TJ, Batko B. Age determines response to anti-TNFα treatment in patients with ankylosing spondylitis and is related to TNFα-producing CD8 cells. *Clin Rheumatol* 2018;**37**:1597-604.
22. Huang F, Gu J, Zhu P, Bao C, Xu J, Xu H, et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial. *Ann Rheum Dis* 2014;**73**:587-94.
23. Hu Z, Xu M, Li Q, Lin Z, Liao Z, Cao S, et al. Adalimumab significantly reduces inflammation and serum DKK-1 level but increases fatty deposition in lumbar spine in active ankylosing spondylitis. *Int J Rheum Dis* 2012;**15**:358-65.
24. Maneiro JR, Souto A, Salgado E, Mera A, Gomez-Reino JJ. Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. *RMD Open* 2015;**1**:e000017.
25. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials: national institute for health and clinical excellence. 2011.
26. Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. *Network meta-analysis for decision-making*. Hoboken, NJ: John Wiley & Sons; 2018.
27. Röver C, Bender R, Dias S, Schmid CH, Schmidli H, Sturtz S, et al. On weakly informative prior distributions for the heterogeneity parameter in Bayesian random-effects meta-analysis. *Research Synthesis Methods* 2021;**12**:448-74.
28. Gelman A. Prior distributions for variance parameters in hierarchical models. *Bayesian Analysis* 2006;**1**:515-33.
29. Medicines and Healthcare products Regulatory Agency. *Tofacitinib (Xeljanz): new measures to minimise risk of venous thromboembolism and of serious and fatal infections*. 2020. Available from: https://www.gov.uk/drug-safety-update/tofacitinib-xeljanz-new-measures-to-minimise-risk-of-venous-thromboembolism-and-of-serious-and-fatal-infections [accessed 17 December 2021]
30. Medicines and Healthcare products Regulatory Agency. *Tofacitinib (Xeljanz): new measures to minimise risk of major adverse cardiovascular events and malignancies*. 2021. Available from:

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

https://www.gov.uk/drug-safety-update/tofacitinib-xeljanzv-new-measures-to-minimise-risk-of-major-adverse-cardiovascular-events-and-malignancies [accessed 17 December 2021]
31. Burmester G, Cohen S, Winthrop K, Nash P, Rubbert-Roth A, Deodhar A, et al. Long-term safety profile of upadacitinib in patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis [abstract]. *Arthritis Rheumatol* 2021;**73 (suppl 10)**.
32. British National Formulary. *BNF*. 2021. Available from: https://bnf.nice.org.uk/ [accessed 23 April 21]
33. National Institute for Health and Care Excellence. *TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Technology appraisal guidance [TA383]*. London: NICE; 2016.
34. Curtis L BA. *Unit costs of health and social care 2019.* In. Kent, UK: Personal Social Services Research Unit; 2019. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/
35. Emery P, Van Keep M, Beard S, Graham C, Miles L, Jugl SM, et al. Cost effectiveness of secukinumab for the treatment of active ankylosing spondylitis in the UK. *Pharmacoeconomics* 2018;**36**:1015-27.
36. Yahya F, Gaffney K, Hamilton L, Lonsdale E, Leeder J, Brooksby A, et al. Tumour necrosis factor inhibitor survival and predictors of response in axial spondyloarthritis-findings from a United Kingdom cohort. *Rheumatology (Oxford)* 2018;**57**:619-24.
37. NHS England. *NHS reference costs 2019 to 2020*. 2020. Available from: https://www.england.nhs.uk/national-cost-collection [accessed 27 November 2020]
38. NHS England. *National cost collection for the NHS, 2019/20 national cost collection data version 2*. 2021. Available from: https://www.england.nhs.uk/wp-content/uploads/2021/06/2_National_schedule_of_NHS_costs_FY19_20_V2.xlsx [accessed 03 February 2022]
39. Abubakar I, Lalvani A, Southern J, Sitch A, Jackson C, Onyimadu O, et al. Two interferon gamma release assays for predicting active tuberculosis: the UK PREDICT TB prognostic test study. *Health Technol Assess* 2018;**22**:1-96.
40. Pareek M, Bond M, Shorey J, Seneviratne S, Guy M, White P, et al. Community-based evaluation of immigrant tuberculosis screening using interferon γ release assays and tuberculin skin testing: observational study and economic analysis. *Thorax* 2013;**68**:230.
41. Curtis LAB, Amanda. *Unit costs of health & social care 2020*. In. Kent: Personal Social Services Research Unit; 2020. Available from: https://kar.kent.ac.uk/84818/13/Unit_Costs_of_Health_and_Social_Care_2020%20%281%29.pdf
42. NHS England. *National cost collection for the NHS, 2019/20 national cost collection data*. 2021. Available from: https://www.england.nhs.uk/wp-content/uploads/2021/06/National-schedule-of-NHS-costs-FY1920-v15.xlsx [accessed date unspecified]

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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

Copyright 2025 King's Printer and Controller of HMSO. All rights reserved.

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.