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Evidence Review Group's Report

Fast Track Appraisal – cost comparison

Tofacitinib for treating active ankylosing spondylitis [ID3865]

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Mark Corbett, Research Fellow, CRD, University of York Ruth Walker, Research Fellow, CRD, University of York Sumayya Anwer, Research Fellow, CRD, University of York Lucy Beresford, Research Fellow, CRD, University of York Matthew Walton, Research Fellow, CRD, 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 Ana Duarte, Research Fellow, CHE, 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 135431.

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 is co-director of an education company (Spondyloarthritis Training and Education SPATE (UK) Ltd.) which hosts medical education meetings for doctors, nurses and physios with pharma sponsors (including AbbVie). However, Sponsors do not contribute to the selection of faculty, programs, talk content or slide review and their products are not promoted during

the talks or education sessions. More information is available at https://rheumatologyevents.org.
We are grateful to Connor Evans for proof-reading a draft version of this report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Corbett M, Walker R, Anwer S, Beresford L, Walton M, Fulbright H, Phung H, Soares M, Rothery C, Duarte A, Dias S. Tofacitinib for treating active ankylosing spondylitis: A Fast Track Appraisal. CRD and CHE Technology Assessment Group, University of York, 2022.

Contributions of authors

Mark Corbett wrote the critique of the decision problem and clinical effectiveness and safety evidence. Ruth Walker contributed to the critique of the decision problem and safety evidence (discontinuation rates). Sumayya Anwer and Lucy Beresford contributed to the critique of the network meta-analyses. Helen Fulbright wrote the critique of the search strategies. Matthew Walton contributed to the critique of the economic evidence. Han Phung performed the validation of the models and outputs. Ana Duarte contributed to the critique of the economic evidence, conducted the economic analyses and took overall responsibility for the economic 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

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List of abbreviations

AE	Adverse event
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath AS Metrology Index
bDMARD	Biologic DMARD
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BSRBR	British Society for Rheumatology Biologics Register
CFB	Change from baseline
CI	Confidence interval
CMU	Commercial Medicines Unit
CrI	Credible interval
CRP	C-reactive protein
CS	Company submission
CSR	Clinical study report
DIC	Deviance information criterion
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
DSU	Decision Support Unit
EMA	European Medicines Agency
ERG	Evidence review group
FDA	Food and Drug Administration
FE	Fixed effects
FTA	Fast track appraisal
GP	General practitioner
HCHS	Hospital & community health services
HLA-B27	Human leukocyte antigen-B27
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology appraisal
IBD	Inflammatory bowel disease
IGRA	Interferon gamma release assay
IL-17A	Interleukin 17A
ITC	Indirect treatment comparison
IV	Intravenous
JAK	Janus kinase
MA	Meta-analysis
MACE	Major adverse cardiovascular events
MCS	mental component score
MD	Mean difference
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction

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
PsA	Psoriatic arthritis
PSSRU	Personal Social Services Research Unit
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QFT-GIT	QuantiFERON-TB Gold-In Tube
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RE	Random effects
RoB	Risk of bias
SAE	Serious adverse event
SC	Subcutaneous
SF-36	Short form health survey
SF-36v2	36-Item Short Form Survey
SmPC	Summary of product characteristics
SR	Systematic review
STA	Single technology appraisal
TB	Tuberculosis
TNF	Tumour necrosis factor
TSD	Technical Support Document
VAS	Visual analogue scale
VTE	Venous thromboembolism

EVIDENCE REVIEW GROUP REPORT: FAST TRACK APPRAISAL (FTA)

1 SUMMARY OF THE ERG'S VIEW OF THE COMPANY'S FTA CASE

1.1 Safety of tofacitinib

Tofacitinib carries a Medicines and Healthcare products Regulatory Agency (MHRA) safety warning, stating that unless there are no suitable treatment alternatives it should not be used in patients with cardiovascular, malignancy or other specific risk factors. This is due to an increased risk of major adverse cardiovascular events (MACE), malignancies, pulmonary embolism, deep vein thrombosis, venous thromboembolism (VTE), serious infections and all-cause mortality in at-risk patients. Based on these risk factors, estimates suggest that at least half the ankylosing spondylitis (AS) patients eligible for tofacitinib should only receive it if there are no suitable treatment alternatives. Of the remaining patients there is uncertainty about what proportion will develop risk factors in the future (e.g. starting smoking) and about whether tofacitinib might contribute to the development of some risk factors (as opposed to exacerbating existing ones). The submission safety data did not allay these concerns because long-term data in AS are not available. The safety data, therefore, do not appear to support the claim that tofacitinib's safety profile is similar to biological disease modifying anti-rheumatic drug (bDMARD) comparators.

1.2 Pathway position and comparators

Based on the safety warnings, the first-line positioning of tofacitinib in the company's submission and the use of adalimumab as a comparator does not seem appropriate and is very unlikely to reflect how tofacitinib will be used in the National Health Service (NHS). Although secukinumab and ixekizumab were subsequently added as comparators at clarification stage, clinician feedback, coupled with the MHRA safety warning, suggest that tofacitinib will likely be used as a new line of therapy in most patients. The evidence review group's (ERG's) advisers also thought that tofacitinib could sometimes displace the use of a second interleukin-17A (IL-17A) inhibitor or, very rarely, be used as a first-line treatment in needle-phobic patients.

If used as a new line of therapy (i.e. the last line of therapy), the relevant comparator would be established clinical management without bDMARDs, which is not listed in the National Institute for Health and Care Excellence (NICE) scope. Established clinical management would not be a suitable comparator for FTA as it would not adequately represent the 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 between tofacitinib and the selected comparators plausible on the basis of the evidence presented, albeit caveated by a number of uncertainties. The company submission (CS) presented network meta-analyses (NMAs) that showed no evidence of differences between tofacitinib and adalimumab and secukinumab in bDMARD- naïve patients and between tofacitinib and secukinumab and ixekizumab in bDMARD-experienced patients.

However, these analyses were limited by failure to include all evidence on tumour necrosis factor-alpha (TNF-alpha) inhibitors, and the small number of studies with few events 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 tofacitinib and comparators, please refer to the confidential appendix. Costs relating to monitoring may have been underestimated for tofacitinib, and costs relating to the treatment of adverse events (AEs) were not included. The magnitude of these costs and their relevance to tofacitinib and 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 in Sections 1.5, 1.6, 1.7 and 1.8. The ERG also notes that the appropriateness of assessing the cost-effectiveness of tofacitinib 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.

1.5 Long-term efficacy: area of uncertainty

The cost comparison necessarily assumes that tofacitinib has similar long-term efficacy to comparators. However, no robust long-term efficacy data was presented to support the assumption of long-term maintenance of treatment response on tofacitinib. 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 tofacitinib were not available (see Section 1.6). Due to the short biological half-life of tofacitinib relative to bDMARDs (hours vs. weeks), adherence issues leading to missed doses of tofacitinib 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 tofacitinib has similar long-term discontinuation to the comparators, and treatment discontinuation due to AEs or loss of response for tofacitinib and comparators is not modelled. However, only very limited data on all-cause discontinuation were

reported for tofacitinib. As a twice-daily orally administered therapy, barriers to treatment adherence may differ compared to monthly subcutaneous (SC) injections. Furthermore, loss of efficacy over time due to adherence issues or other as yet uncharacterised reasons may lead to differences in long-term rates of discontinuation. The implications of differential rates of treatment discontinuation upon the cost-effectiveness of tofacitinib 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 treatment discontinuation for tofacitinib 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 tofacitinib. 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 tofacitinib. 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 tofacitinib and comparators cannot be accounted for 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 tofacitinib differs to that of the comparators, this exclusion would have uncertain implications upon the relative cost-effectiveness of tofacitinib.

2 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

The positioning proposed in the main CS was in line with tofacitinib's marketing authorisation, i.e. used as first or subsequent line of therapy. The company stated that there is a clear unmet need for further options in the treatment of AS. Adalimumab was the chosen comparator. However, after clarification the company presented analyses comparing tofacitinib with secukinumab in bDMARD-naïve patients and comparing tofacitinib with secukinumab and ixekizumab in bDMARD-experienced

patients, stating that this was "*for completeness and in order to remove the uncertainty around the use of tofacitinib in subsequent lines of therapy*".

2.1 Relevant decision-problem according to NHS practice and the NICE scope

Population

The ERG's clinical advisers noted that in October 2021 the MHRA issued a safety warning about tofacitinib, advising that unless there were no suitable treatment alternatives, tofacitinib should not be used in patients with any of the following risk factors: over 65 years of age, current/past smokers, VTE risk factors, cardiovascular (such as diabetes or coronary artery disease) risk factors or malignancy risk factors (see Section 3.3).[1] For the purposes of this appraisal, this safety warning[1] effectively restricts the population to a subset of the population defined in the NICE scope (i.e., those who are younger than 65 years of age, never smokers, and without VTE, cardiovascular, or malignancy risk factors), but the clinical evidence provided by the company in support of the assumption of equivalent effectiveness and safety profile of tofacitinib and comparators in the cost comparison was generated in an unrestricted population. In light of this, the ERG asked the company to comment on the representativeness of the trial populations in relation to those currently eligible for treatment, and any implications for trial effect estimates. In the point for clarification response the company said it did not anticipate this issue to substantially affect the population addressed in the appraisal or the decision problem. The company presented data on patients with at least 40% improvement in the Assessment of SpondyloArthritis International Society scale (ASAS40) showing similar efficacy in subgroups based on smoking status (and other risk factors). The ERG notes that the evidence presented is limited in terms of outcomes so does not sufficiently resolve the uncertainty on this issue. It is also unclear whether any patient characteristics are effect modifiers. The company also provided tofacitinib clinical trial and British Society for Rheumatology Biologics Register (BSRBR) data which indicated that around 25-30% of AS patients were current smokers, 16-33% were former smokers, 11-20% had hypertension and 3-5% had diabetes. Tofacitinib's summary of product characteristics (SmPC) states that it should be used with caution in patients with known risk factors for VTE regardless of indication and dosage. One of the risk factors is obesity; in pivotal study A3921120, 23% of patients had a body mass index (BMI) of $\geq 30 kg/m^2$. Estimates therefore suggest that, based on the MHRA guidance on restricted use and tofacitinib's SmPC, at least half the AS patients eligible for tofacitinib should only receive it if there are no suitable treatment alternatives, i.e. as a last line of therapy. Moreover, of the remaining patients (those not currently with risk factors for serious adverse events (SAEs)) there is uncertainty about:

- What proportion will have risk factors in the future e.g. starting smoking, development of hypertension and,

- Whether tofacitinib might be the cause of the development of some risk factors (as opposed to exacerbating existing risk factors).

This further reduces the proportion of the AS population for which first-line tofacitinib treatment is appropriate. Therefore, in terms of clinical trial evidence, the most relevant population is patients who have already taken one or more bDMARDs (rather than bDMARD-naïve patients) for whom there is limited trial evidence. Only one of the two tofacitinib trials included bDMARD-experienced patients (study A3921120) and in this study only 23% of patients had previously taken a bDMARD therapy. This limits the applicability of the tofacitinib trial populations to an NHS setting.

Comparators

Adalimumab (in biologic-naïve patients) was the only comparator considered in the CS. At the clarification stage, the ERG requested the company to comment on how the MHRA safety issues may affect the pathway position of tofacitinib in the NHS. In its response the company presented NMAs comparing tofacitinib with secukinumab in bDMARD-naïve patients and comparing tofacitinib with secukinumab and ixekizumab in bDMARD-experienced patients. The company compared the costs of secukinumab 150mg and secukinumab 300mg (for patients for whom dose is increased to 300mg according to clinical response after 16 weeks with secukinumab 150 mg). The company did not present clinical evidence to support the comparison with secukinumab 300mg (see Section 3.2.3). Secukinumab 300mg has also not been recommended by NICE.[2] Therefore, when discussing the appropriateness of secukinumab as a comparator, the ERG refers specifically to secukinumab 150mg.

The ERG asked their two clinical advisers which biologic 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 therapy. Generally, a TNF-alpha inhibitor would be tried first, usually followed by either a second TNF-alpha inhibitor or an IL-17A inhibitor. 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. 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 clinical advisers also commented on the anticipated use and positioning of tofacitinib. Table 1 shows that for all patients except those with inflammatory bowel disease (IBD), the ERG's clinical advisers did not foresee tofacitinib being used before the third-line of treatment and they anticipated it being used as the last-line of treatment in many patients. These positionings are based both on the level of confidence in the efficacy and safety profile of TNF-alpha inhibitors and IL-17A inhibitors and on tofacitinib safety concerns about an increased risk of MACE, malignancies, serious VTE and infections (see Section 3.3). For comparison and context, the ERG's advisers described how tofacitinib has been used in the NHS for treating other diseases in adults; although tofacitinib was recommended several years ago by NICE for treating patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA), in the advisers' experience it has been used very little in practice (and seldom at first-line).

The ERG considers that, from a clinical perspective, the most relevant comparators for tofacitinib at third-line of treatment are likely to be ixekizumab and secukinumab, but notes that secukinumab has a greater market share than ixekizumab [redacted] respectively; see Table 1, CS). Since having a significant market share is one of the FTA process criteria to establish the relevant comparator, the ERG considers secukinumab to be the relevant comparator for bDMARD.-experienced patients. The ERG notes that the bDMARD market share data provided by the company (see Table 1, CS) is not reported by line of treatment. Furthermore, the methodology used to estimate the market share of these drugs in AS (see Section B.1.1.2, CS, and company reference pack) is not clearly described. Therefore, there may be uncertainty on whether these estimates are truly reflective of bDMARD use in AS.

The clinical advisers emphasised that variation in tofacitinib use would be expected (in terms of line of treatment), depending on the extent of concerns about the risk of 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. Nevertheless, the company's choice of adalimumab, secukinumab and ixekizumab as comparators appears inappropriate for most patients, based on the MHRA guidance on tofacitinib's restricted use, uncertainties about the development of risk factors when taking tofacitinib, and the ERG's clinical advisers' opinions. In light of this, the most relevant comparator for most (though not all) patients would be established clinical management without biologics, even though this is not a listed comparator in the NICE scope.

Table 1. ERG clinical adviser opinions on comparator use and the anticipated use of tofacitinib

Subpopulation or subgroup of AS patients	ERG clinical advisers' opinions on:	
	The comparators most likely to be used	The anticipated use of tofacitinib

Biologic-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
Biologic-naïve and contraindicated for TNF-alpha inhibitors	Secukinumab or ixekizumab	Very unlikely to be used
No response to first biologic (typically TNF-alpha inhibitor)	Either try another TNF-alpha inhibitor or switch to secukinumab or ixekizumab	3rd line or later
Responded to first biologic (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[3])		
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 (6%)	IL-17A inhibitors are not recommended. Only infliximab, golimumab and adalimumab are licensed for IBD, so are preferred to etanercept.	2nd line or later

Impact of administration preference and medication adherence on pathway position

The CS (page 27) stated that there is an unmet need for an oral therapy and that patients with other rheumatological conditions have been shown to prefer oral therapies over injectables due to ease of administration. The ERG notes that in the study cited in the CS on oral therapy preference[4] (in patients with RA) most patients (60%) had taken oral-only therapies, so many patients were expressing preferences after experiencing only one mode of administration. This limitation may also reduce the study's applicability to an AS population in which many patients have already received injectable treatments. The study found that those taking an oral-only therapy were almost nine times more likely than those on an intravenous (IV) or SC therapy to prefer oral administration. The study was also limited in that it did not record strength of preference.

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 very few patients would receive tofacitinib at the first-line of treatment as a result of being needle-phobic. In their experience, very few patients were needle-phobic, and patients who disliked needles could tolerate monthly injections. Adalimumab requires maintenance injections once every two weeks (Q2W) and secukinumab and ixekizumab are

administered monthly. Following initial training from a healthcare professional, they may be self-administered at home by the patient. The ERG's advisers thought that such comparators were unlikely to be too much more burdensome to most 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 a self-administrable injectable (and often delivered cost-free within patient programmes led by companies who manufacture bDMARDs).

The ERG's clinical advisers also thought that adherence and compliance with a twice-daily tablet may possibly be problematic for some patients. For example, younger people of working age may forget to take a tablet during the day and older patients may have reduced adherence as a result of polypharmacy issues (i.e. they may have too many prescribed tablets to remember to take them all). Week 16 analysis (up to 48 weeks) of compliance with tofacitinib 5mg was reported for trial A3921120 (clinical study report (CSR) Table 14.4.1.9**)**. At 16-week follow-up, cumulative incidence of under-compliance is reported as [redacted] at 16-weeks follow-up and [redacted] at 48-weeks follow-up (Table 14.4.1.9 CSR**)**. For trial A3921119 non-compliance (<80% compliance overall) was reported as [redacted] for 5mg tofacitinib (CSR Table 14.1.7.1). In practice, clinical monitoring of adherence to tablets is also likely to be more difficult than that of adherence to biologic therapies. The ERG also notes that due to the biological half-life of tofacitinib, missed doses, treatment interruptions, and other issues leading to reduced adherence may have a greater effect upon the drug's efficacy compared to the less frequently administered SC biologics. The ERG considers this to have been inadequately explored.

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

The first-line positioning of tofacitinib in the company's submission and the use of adalimumab as comparator does not seem appropriate and is very unlikely to reflect how tofacitinib will be used in the NHS. The addition to the submission of secukinumab and ixekizumab as comparators is welcomed, although it would appear that tofacitinib is most likely be used as a new line of therapy (or to displace a second IL-17A inhibitor). If used as a new line of therapy, as appears likely for most patients (based on clinical advice), then the relevant comparator would be established clinical management without biologics, which is not listed in the NICE scope. Established clinical management would not be a suitable comparator for FTA as it would not adequately represent the NICE recommended treatments as a whole in terms of cost and effects. Furthermore, the use of tofacitinib as an additional line of therapy implies a potential impact to downstream costs and HRQoL

outcomes of managing the condition, which can only be captured by explicitly modelling subsequent lines of treatment in a cost-utility framework.

The introduction of an oral medication for treating AS is useful, although it is unlikely to change choice-of-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 adult patients with AS. A description of the searches and the search strategies were included in Appendix D of the CS (pages 10-12). In response to the ERG's clarifications, a further document was provided by the company, which included additional search strategies and clarifications. The ERG's appraisal of the searches is presented in Table 2.

Table 2. ERG Appraisal of Evidence Identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	Update Searches Missing: The update searches were not included in the original CS but were provided in the response to clarifications. Confusing Representation of Hits The total number of hits shown for each line in the search strategy varies between using: * Duplicates are removed from the search but included in the result count. ° Duplicates are removed from the search and from the result count. This suggests that de-duplication has been performed on a line-by-line basis which makes it confusing to understand the number of hits retrieved by the search strategy overall. Normally, the total hits retrieved would be stated (for each line and overall) and the combined total would then be adjusted to show the number of hits after de-duplication.
Were appropriate sources searched?	PARTLY	Limited Sources Searched A limited number of databases were searched i.e., a multifile search of two databases, Medline and Embase, conducted via ProQuest. Conference proceedings, health technology appraisal (HTA) literature sources, grey literature sources and trials registry databases were not searched for in their own right using specialised databases. This was raised at the clarification stage. Although the company response clarified that prior HTA submissions were reviewed; conference proceedings were searched for additional information; and randomised controlled trials (RCTs) published only as abstracts were not targeted for inclusion; the concern represented by the ERG in the clarification stage still stands. The original CS describes that '[a] comprehensive systematic literature search was implemented to identify all available literature…' (Appendix D, page 10) and this is inaccurate. However, in the response to clarifications the company made assurances that they compared their results with those of previous NICE technology appraisals and they are not aware of any studies that were missed.

Was the timespan of the searches appropriate?	YES	No date limits were placed on the search.
Were appropriate parts of the PICOS included in the search strategies?	YES	Population AND Intervention AND Study Type.
Were appropriate search terms used?	PARTLY	Missing Trade Names for Drugs: Strategies are missing the biosimilars of adalimumab – Amsparity, Cyltezo, Halimatoz, Kromeya, Solymbic, Yuflyma and biosimilars of etanercept – Nepexto and Lifmior. This was raised as a clarification. The company responded that these biosimilars were not included as they are unlikely to be compared to placebo alone. Missing Terms for Condition ankylosing spondylarthritides, ankylosing spondylarthritis, ankylosing spondyloarthritides, ankylosing spondyloarthritis, bechterew disease, bechterew's disease, bechterews disease, marie struempell disease, marie-struempell disease, rheumatoid spondylitis, ankylating spondylitis, ankylopoietic spondylarthritis, ankylopoietic spondylitis, ankylosing spine, ankylosing spondilitis, ankylosing spondylarthritis, ankylosing spondylarthrosis, ankylosis spondylitis, ankylotic spondylitis, bekhterev disease, morbus bechterew, spinal ankylosis, spine ankylosis, spondylarthritis ankylopoietica, spondylarthritis ankylosans, spondylarthrosis ankylopoietica, spondylitis ankylopoetica, spondylitis ankylopoietica, spondyloarthritis ankylopoietica, vertebral ankylosis The limited coverage of terms used for the condition risks missing relevant material. However, in the response to clarifications the company made assurances that they compared their results with those of previous NICE technology appraisals and they are not aware of any studies that were missed. Lack of Subject Headings / Missing Subject Headings: It is best practice in literature searching to represent each concept through a choice of subject headings or textwords, in order to capture papers with subject headings but no abstract, as well as papers with an abstract but no subject headings. However, there are no MeSH terms or Emtree terms for any the Intervention terms represented in line number S2 despite the existence of such terms. The following are all Emtree headings which could have been used: etanercept, infliximab, adalimumab, golimumab, certolizumab pegol, secukinumab, ustekinumab, ixekizumab, netakimab, apremilast, bimekizumab, upadacitinib, filgotinib, etoricoxib, tofacitinib. The following are MeSH headings which could have been used: Etanercept, Infliximab, Adalimumab, Certolizumab Pegol, Ustekinumab, Etoricoxib. This was raised as a clarification and the company clarified that they were looking for treatment names that were specifically referred to in the title or abstract. The company made assurances that they compared their results with those of previous NICE technology appraisals and they are not aware of any studies that were missed.
Were any search restrictions applied appropriate?	PARTLY	Publication Bias Unclear Table 1 (page 10, Appendix D) of the PICOS Framework for Structuring the Literature Search specifies that non-English language papers will be excluded. This limit does not appear in the search strategy, and it is unclear if this limit was part of the search strategy or the screening criteria. This is an important distinction as many reviews that use this exclusion criteria use it as part of the screening process only, so as not to rely on the accuracy of the metadata applied on the database. This was raised as a clarification. The company response was that non-English language papers are typically excluded from literature searches. However, it is still not clear how this exclusion was applied.
Were any search filters used validated and referenced?	UNCLEAR	Study filters may have been used to limit to RCTs, systematic reviews (SRs) or meta-analyses (MAs) in the multifile search of Medline and Embase via ProQuest. However, these are not reported or referenced in the CS.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

3.1.2 Screening, data extraction and quality assessment methods

The systematic review methods were described in Appendix D of the CS. No details were reported about the processes of title and abstract and full-text screening (e.g. such as researchers screening independently), therefore the possibility of errors and bias affecting the selection of studies cannot be ruled out.

The bibliographic database search strategies were designed to identify all the comparator interventions listed in the NICE scope. However, at the full-text screening stage of the systematic review, studies which were not of either tofacitinib or adalimumab were excluded. It is unclear why the company adopted this approach, rather than either including studies of all eligible comparators (having searched for them) or instead searching only for studies of adalimumab and tofacitinib. Moreover, restricting the review to only one comparator (adalimumab) meant there was no flexibility to allow comparisons with other biologics, if these were considered more appropriate. This is an important limitation of the company's systematic review, given the ERG's request for comparisons of tofacitinib versus IL-17A inhibitors in biologic-experienced patients. This request was specifically based on the ERG's clinical advisers stating that it was very unlikely that patients would take tofacitinib as a first-line (or even second-line) therapy. These comparators were later included in response to clarification (see Section 3.1.3), but the company did not provide details on the processes used to identify the relevant studies or extract the data.

The CS stated that the quality assessments were undertaken using the updated version of the Cochrane risk of bias tool (RoB 2), according to the tool's full guidance document. The results from the risk of bias assessment are reported in Table 7 of the appendix C-I. Only one study, Hu et al. 2012,[5] was deemed overall to be high risk of bias, due to selection of reported results. However, no details to support the judgements were reported, which limited the transparency of the assessment results. No risk of bias assessments were carried out for the additional studies included at the clarification stage.

3.1.3 Included trials

The review included seven RCTs (covered across nine publications), all of which were placebo-controlled trials of tofacitinib or adalimumab. However, the company did not include its own large randomised safety trial (called 'ORAL Surveillance') of tofacitinib versus TNF-alpha inhibitors. Although this trial was in RA patients, its primary outcomes were AEs and its results have important implications for any adults taking tofacitinib (see Section 3.3).

3.2 Clinical effectiveness of tofacitinib

3.2.1 Methods of study A3921119 and study A3921120

Tofacitinib (5mg) was compared to placebo in two multicentre, randomised trials. Study A3921119 was a phase 2 dose-ranging trial in 103 biologic-naïve patients and study A3921120 was a phase 3 trial of 207 biologic-naïve and 62 biologic-experienced patients.

Assessments were made at 12 weeks in study A3921119 and 16 weeks in study A3921120. However, 16 weeks was the timepoint specified for the primary and secondary outcomes in the pivotal phase 3 trial (A3921120). The CSR for study A3921120 indicated that

[redacted]

The quality assessments of the two trials were reported in Table 13 of the CS with the company considering the risk of bias in both trials to be low. The ERG was able to corroborate the low risk of bias judgements for all domains (although limited method details were available on blinding). However, the CS did not include an evaluation of the applicability of the trial results. The ERG notes that a limited number of bDMARD-experienced patients were recruited to the tofacitinib trials, with evidence available for only 62 such patients from study A3921120. There is also uncertainty about what impact the presence of cardiovascular risk factors have on efficacy, especially in the longer-term (around half the trial patients have a cardiovascular risk factor which may increase the risk of an SAE). Notwithstanding these issues, the ERG's clinical advisers thought that both the trial eligibility criteria and baseline characteristics were adequately representative of patients seen in NHS practice.

3.2.2 Results of study A3921119 and study A3921120

In both studies, tofacitinib was statistically significantly more effective than placebo for all the key outcomes listed in the NICE scope. Following a clarification question the company stated that extra-articular manifestation outcomes (listed in the NICE scope) were reported as safety events and were not part of the primary or secondary endpoints of the trials. The available data on this were also presented (clarification question A8, Table 11);

[redacted]

Subgroup results

In a clarification point, the ERG requested subgroup analyses based on prior biologic use with results to be presented as risk ratios or mean differences (MDs) with 95% confidence intervals (CIs). The company did not provide risk ratios for the binary outcomes, although the results provided were limited by low numbers of patients and events in the biologic-experienced subgroup. For the continuous outcomes at 16 weeks, tofacitinib [redacted] The ERG agrees though with the company's statement that these results should be interpreted with caution as the study was not powered to detect differences in subgroups by prior biologic treatment.

Long-term efficacy

Given the different mechanism of action to bDMARDs, a key area of uncertainty is the longer-term efficacy of tofacitinib and the length of time patients may sustain a treatment response. Although some patients can develop anti-drug antibodies to bDMARDs which affects efficacy, the ERG's clinical advisers stated that, in theory, patients would not develop antibodies to Janus kinase (JAK) inhibitors (as they are small molecules). However, the ERG's advisers thought there was insufficient evidence to speculate on the long-term effectiveness of tofacitinib.

3.2.3 Network Meta-Analyses

In the main CS, the company presented NMAs to compare the relative efficacy and safety of tofacitinib to adalimumab in a bDMARD-naïve and a mixed population (including bDMARD-naïve and -experienced patients). A summary of these NMAs is provided in Section B.3.9 and additional details are included in Appendix D. In response to clarification questions, the company also provided NMAs comparing tofacitinib to secukinumab in biologic-naïve patients and to compare tofacitinib with secukinumab and ixekizumab in biologic-experienced patients. Details and results for these additional NMAs are described in the company's clarifications response. The NMAs used fixed and random-effects models with and without baseline-risk adjustments adapting methods described in the NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 2 and 3.[6, 7]

3.2.3.1 Comparison to Previous Appraisals

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 tofacitinib appraisal were broadly similar to the approaches used in previous appraisals, but there were some differences.

Population

The company's approach to modelling the populations is broadly similar to the previous single technology appraisal (STA) of secukinumab and ixekizumab. In TA407 (secukinumab), the NMAs modelled a mixed and a bDMARD-naïve population. In the ixekizumab appraisal (TA718), bDMARD-naïve and -experienced patients were modelled separately and sensitivity analyses were conducted including trials where the population of interest was unclear. 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 large 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 tofacitinib NMAs, the time point of assessment of initial response ranged from 12-16 weeks, and outcomes were pooled across studies. Given that the SmPC for tofacitinib suggests discontinuation if there is no response by 16 weeks, and for consistency with other appraisals, the ERG considers the 16-week data to be the most appropriate when comparing tofacitinib with other treatments in NMAs. This is because this would be the time point for which, in clinical practice, a decision will typically be made to continue with current treatment, or switch to an alternative (see also Section 3.2.1).

The 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 inhibitor drugs also pooled the responses assessed at weeks 10-16.

Selection of outcomes

The tofacitinib NMAs model the most extensive number of outcomes, compared to previous appraisals, and includes the modelling of HRQoL outcomes, and the BASMI score and ASAS20 (which is not included as an outcome in ixekizumab or the MTA of the TNF-alpha inhibitors). In the

additional NMAs provided at clarification stage, the company included Ankylosing Spondylitis Disease Activity Score (ASDAS) and excluded BASMI score CFB as outcomes (Table 3).

Table 3. Outcomes included in the NMAs in the tofacitinib appraisal and previous appraisals for ankylosing spondylitis

Tofacitinib (this appraisal)	TNF-alpha inhibitors (TA383)	Ixekizumab (TA718)	Secukinumab (TA407)
ASAS20 ASAS40 BASDAI50 BASDAI score CFB BASFI score CFB BASMI score CFB SF-36 PCS score CFB SF-36 MCS score CFB ASQoL score CFB ASDAS	BASDAI50 BASDAI score CFB BASFI score CFB	ASAS20ASAS40 BASDAI50 BASDAI score CFB BASFI score CFB	ASAS40 BASDAI50 BASDAI score CFB BASFI score CFB

MCS: mental component score; PCS: Physical component score; SF-36: 36-Item Short Form Survey

The company present a cost-comparison analysis and argue that tofacitinib has similar efficacy, safety and quality of life (QoL) outcomes to adalimumab, secukinumab and ixekizumab for all outcomes considered relevant in previous appraisals.

Fixed/Random Effects Models

In their submission, the company selected unadjusted random effects (RE) models to compare tofacitinib to adalimumab for all outcomes due to the perceived heterogeneity in the data. However, as the difference between the deviance information criterions (DICs) for the fixed effect (FE) and RE models was less than three for all outcomes, the ERG prefers the simpler FE model instead as recommended by the NICE DSU TSD2.[6] Additionally, as there were few studies per comparison in the network for each outcome, there likely is insufficient evidence to estimate the between study heterogeneity.[8-10] In their response to clarifications, the company expressed neutrality about selecting RE models over FE and considered the results of both "informative and suitable for decision-making" as the results for both models were very similar for all outcomes. In the additional NMAs comparing tofacitinib to secukinumab and ixekizumab, the company selected the simpler FE model. Previous appraisals have also favoured FE models.

Placebo or Baseline-Adjustment

The company also explored placebo-adjusted comparisons where there was enough data available. The company present the results for the FE and RE models with baseline risk adjustment in the Appendix D in the CS. Placebo-response adjustments were also explored in previous appraisals (TA407 and TA383) but were often not appropriate due to data sparsity. The company also experienced poor convergence when fitting some placebo-adjusted models due to the low number of

studies. Including other TNF-alpha inhibitors in the network could have improved estimation of the placebo-adjusted models.

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 class effect model was found to produce a better-fitting model compared to the models that assumed independent treatment effects, and were used in the economic model.[11] There was clinical support for this assumption and, in light of the available evidence, it was considered reasonable for decision-making purposes.

The STA of secukinumab (TA407) did not consider 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 axial spondyloarthritis 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.[12]

In the original CS, tofacitinib did not consider an NMA assuming class effects for TNF-alpha inhibitors. At the clarification stage, the ERG also asked the company to comment on the plausibility of a class effect for effectiveness and safety across other JAK inhibitors (including upadacitinib and filgotinib). The company did not comment on the class effect owing to the paucity of head-to-head or indirect treatment comparisons (ITCs) for JAK inhibitors. The company also did not consider it appropriate to consider a class effect for TNF-alpha inhibitors as they did not consider that the conclusions about the efficacy of tofacitinib against adalimumab would change. The company stated that adalimumab was the only relevant TNF-alpha inhibitor because in previous appraisals committees have concluded that TNF-alpha inhibitors should be considered as a class with broadly similar, even if not completely identical, effects (TA383, TA407). However, the ERG is concerned that failure to include all the evidence on TNF-alpha inhibitors in the network and assuming that adalimumab alone can be considered to represent the average class effect is a limitation. Models previously used to model the effect of TNF-alpha inhibitors and to compare them as a class (TA383[11]) have shown that adalimumab has the lowest effect in the class when compared to placebo. Therefore, it is questionable whether a network including only adalimumab can be considered to adequately estimate the TNF-alpha inhibitor class effect, as claimed by the company. The ERG argues that excluding other TNF-alpha inhibitors from the NMA will underestimate the effectiveness of TNF-alpha inhibitors as a class and increase the uncertainty in the estimates, favouring tofacitinib.

3.2.3.2 Studies included in the NMA

Initially, the company only included studies comparing tofacitinib or adalimumab in their network. Studies comparing secukinumab and ixekizumab were also included after the clarification stage.

The ERG also requested that an expanded network including all evidence on TNF-alpha inhibitors be considered but this was not done by the company. Including other TNF-alpha inhibitors such as etanercept, certolizumab pegol, golimumab, or infliximab in the network would have allowed for a class effect model to be used which would generate more robust estimates by allowing information to be borrowed from other treatments within the same class. The reasons provided by the company for this refusal did not mitigate any of the points made by the ERG in Section 3.2.3.1.

Although the company states that NMAs were conducted on two sub-populations based on previous biologic experience: (i) treatment-naïve patients, and (ii) a mixed population, it is important to note that the evidence available for an NMA of a mixed population is very limited. All adalimumab trials were conducted on treatment-naïve patients, while only one trial for tofacitinib (A3921120) included patients with prior biologic experience (only 62 patients with prior biologic experience were recruited). The ERG notes that the NMA carried out on the mixed population is not representative of a truly mixed population, given that all adalimumab evidence is on naïve patients and only a small proportion of the evidence on tofacitinib is on biologic-experienced patients.

All of the adalimumab trials were included in NICE TA383 except COAST-V which was published after TA383. In response to clarification question A13, the company also included evidence on four additional trials comparing secukinumab and ixekizumab to placebo in additional NMAs for the bDMARD-naïve and -experienced subpopulations. A list of the studies included in each NMA for adalimumab, secukinumab, and ixekizumab are presented in Table 11, in Appendix 1. There were two distinct networks for the bDMARD-naïve population and separate NMAs were conducted: one comparing tofacitinib to adalimumab, and the second comparing tofacitinib to secukinumab, instead of combining both networks and conducting a single NMA to compare the 3 interventions. Given the evidence available, where there are no head-to-head trials comparing adalimumab to secukinumab, the results from the two separate NMAs will be the same as if a single NMA, when the FE model is selected.

Subgroup data from MEASURE 2, MEASURE 4, and MEASURE 5 were included in NMAs for bDMARD-naïve and bDMARD-experienced populations. The COAST-W study only provided evidence on ixekizumab for a biologic-experienced population.

3.2.3.3 Potential Causes of Heterogeneity in the NMAs

Due to the limited number of studies included in the NMAs, the level of heterogeneity present in each network could not be reliably estimated for all outcomes. In addition, the structure of the networks for all outcomes means that there is no potential for detecting inconsistency as there is no independent, indirect evidence for any of the comparisons (loops are formed of multi-arm trials only).[13]

The company considers the trials included in the NMAs comparing the efficacy of tofacitinib against adalimumab to be relatively homogenous. The eligibility criteria of the included studies were similar, with all studies recruiting participants with BASDAI scores ≥4, who had failed either a non-steroidal anti-inflammatory drug (NSAID) or DMARD previously. The only exception was one tofacitinib trial which included patients who had previously received a TNF-alpha inhibitor (A3921120). Patients who were bDMARD-experienced in the A3921120 trial were excluded from the NMAs of biologic-naïve patients, but were included in the NMA of the mixed population, and were analysed separately in the additional NMAs comparing tofacitinib to the IL-17A inhibitors. The company do not comment on the similarity of the trials included in their additional NMAs comparing tofacitinib against secukinumab and ixekizumab at the clarification stage. The eligibility criteria of the included studies was comparable, with all trials recruiting participants ≥18 years old with active AS defined as BASDAI ≥4, and spinal pain of over 4cm on a 10cm visual analogue scale (VAS), who had an inadequate response or intolerance to NSAIDs. MEASURE 5 also includes back pain score over ≥40 mm on a 100 mm VAS. The ERG considers that the trials included in the additional NMAs to be relatively homogenous. With the exception of MEASURE-5,[14] (which was published after the ixekizumab appraisal in May 2020) all studies have been included in previous appraisals.

The definition of outcomes across the trials included in the networks are generally consistent and is unlikely to contribute to the heterogeneity.

The company provide data regarding the baseline characteristics of the studies included in the NMA of tofacitinib and adalimumab (Table 9, Appendix D of the CS) and notes that studies are similar, with the exception of Hu (2012),[5] which the company excluded from the NMAs. In Appendix D of the CS, the company note that few baseline and disease characteristics were reported for the Hu (2012) trial of adalimumab. However, the ERG notes that C-reactive protein (CRP) levels, BASDAI and BASFI scores, were reported in TA383[5, 11] where this study was included in the NMAs. The ERG also believe that the population in the Huang (2014)[15] trial is slightly different from the other included studies as patients are considerably younger, have lower BASFI scores and higher levels of CRP at baseline scores, and were more likely to be human leukocyte antigen-B27 (HLA-B27) positive compared to the other trials.[11] These characteristics are known to be predictors of response for patients with AS.[16] Given that the Huang trial is relatively large (n = 344), it could have an impact on the results.

For the additional models comparing tofacitinib against secukinumab and ixekizumab presented at clarification, the company did not provide an overview of the baseline characteristics of each included study. Overall, the baseline characteristics are relatively homogenous across the trials, although some of the baseline characteristics are not reported separately for bDMARD-naïve and -experienced patients in the MEASURE 4 and 5 trials. The time since diagnosis was lower in the MEASURE 5 (secukinumab at 150mg) and in the A3921120 (tofacitinib) trial. The company do not provide a standard deviation around the mean for the time since diagnosis in the A3921120 trial, so it is difficult to quantify the extent of heterogeneity in this variable for the patients included in the trial. The proportion of participants who were male is higher in the A3921120 and MEASURE 5 trials compared to the other studies included in the networks, which is a predictor of response in patients with AS.[16] Finally, patients in the MEASURE 5 study were considerably younger compared to patients included in the other trials. Given that trials of both tofacitinib and secukinumab have patients with baseline characteristics that are known to be predictors of response (including age and proportion of participants that were male), there is uncertainty surrounding the impact that these differences may have on the network, and whether it biases one treatment over the other. However, in previous appraisals it was accepted that studies could still be pooled in NMAs.

The time point of assessment of response is relatively similar across the trials included in the NMAs in the original CS. COAST-V (adalimumab) and A3921120 (tofacitinib) have assessment at 16 weeks as do the ixekizumab and secukinumab trials. The time point of assessment of response could impact results as participants are more likely to respond if the initial assessment of response is later.[17, 18] However, the time points used agree with previous appraisals (see Section 3.2.3.1) where it had a minimal impact on heterogeneity.

3.2.3.4 Results of the NMAs presented in the company submission

bDMARD-naïve population

Efficacy outcomes

Table 4 reports the results of the models preferred by the ERG for the efficacy outcomes. Credible intervals (CrIs) for all estimates included the null effect, therefore there was insufficient evidence to suggest a difference in treatment effects for tofacitinib compared to adalimumab or secukinumab. Forest plots comparing tofacitinib and adalimumab provided by the company in their response to clarification demonstrated that results are similar, irrespective of the final model selected.

Table 4. Results of ERG-preferred models for efficacy outcomes (bDMARD-naïve patients)

	NMA in Company Submission			NMA in Response to clarifications		
Outcome	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Adalimumab**	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Secukinumab (Loading Dose)**

OR (95% CrI)[a]						
ASAS20	6	FE	[redacted]	5	FE	[redacted]
ASAS40	6	FE	[redacted]	5	FE	[redacted]
BASDAI 50	4	FE	[redacted]	N/A	N/A	N/A
MD (95% CrI)[b]						
BASDAI CFB	6	FE*	[redacted]	5	FE	[redacted]
BASFI CFB	5	FE	[redacted]	N/A	N/A	N/A
BASMI CFB	5	FE	[redacted]	Outcome was not reported in the NMA		
ASDAS	Outcome was not reported in the NMA			N/A	N/A	N/A

[a] null effect is 1; [b] null effect is zero. N/A: This NMA was not conducted as there was no evidence available for this comparison. * The FE baseline-adjusted model had a smaller DIC (FE: 11.079, FE baseline-risk-Adjusted: 5.563).
Abbreviations: CFB: change from baseline, CrI: credible interval, DIC: deviance information criterion, FE: fixed effect, MD: mean difference, NMA: network meta-analysis, OR: odds ratio.

Quality of life outcomes

Table 5 reports the results for the models preferred by the ERG for QoL outcomes for the comparisons of tofacitinib to adalimumab and secukinumab. Only FE models could be fit for the Ankylosing spondylitis quality of life (ASQoL) CFB outcome due to the low number of studies in both networks.

CrIs for the estimates of all outcomes included the null effect, therefore there was insufficient evidence to suggest a difference in QoL between tofacitinib and adalimumab and secukinumab. Results for the only QoL outcome for which the baseline-risk adjusted model was fit, 36-Item Short Form Survey (SF-36v2) mental component score (MCS) CFB (for the tofacitinib vs. adalimumab comparison), were consistent with the unadjusted model. Forest plots comparing tofacitinib to adalimumab provided by the company in their response to clarifications demonstrated that the results would be similar, irrespective of the final model selected.

Table 5. Results of ERG-preferred unadjusted models for QoL outcomes (bDMARD-naïve patients)

	NMA in Company Submission			NMA in Response to clarifications		
Outcome	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Adalimumab**	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Secukinumab (Loading Dose)**
MD (95% CrI)[a]						
ASQoL CFB	3	FE*	[redacted]	5	FE*	[redacted]
SF-36v2 PCS CFB	5	FE	[redacted]	5	FE BL-adj*	[redacted]
SF-36v2 MCS CFB	4	FE**	[redacted]	Outcome was not reported		

[a] null effect is 0. * RE analysis not conducted due to poor convergence. ** The baseline-risk adjusted models for this NMA did not converge.
Abbreviations: BL-Adj: baseline-risk adjusted, CFB: change from baseline, CrI: credible interval, FE: fixed effect, MD: mean difference, NMA: network meta-analysis, OR: odds ratio.

Adverse event outcomes

No NMAs of AEs were conducted on a bDMARD-naïve population as there was no subgroup data available based on prior biologic-experience. NMAs on AEs were conducted for mixed population; the results are reported in Section 3.3.

bDMARD-experienced population

Efficacy outcomes

Table 6 reports the results of the models preferred by the company and the ERG for the efficacy outcomes. Due to the low number of studies the company did not fit baseline-risk adjusted models for any of the outcomes. CrIs for the estimates for all outcomes included the null effect, therefore there was insufficient evidence to suggest a difference in treatment effects for tofacitinib compared to secukinumab and ixekizumab. The CrIs for the odds ratios estimated for ASAS20, ASAS40 and BASDAI50 were very wide, reflecting large uncertainty in the estimates.

Table 6. Results of ERG-preferred models for efficacy outcomes (bDMARD-experienced patients)

Outcome	Number of Studies	Selected Model	Tofacitinib vs. Secukinumab (Loading Dose)	Tofacitinib vs. Ixekizumab
			OR (95% CrI)[a]	
ASAS20	5	FE	[redacted]	[redacted]
ASAS40	5	FE	[redacted]	[redacted]
BASDAI 50	2	FE	[redacted]	[redacted]
			MD (95% CrI)[b]	
BASDAI CFB	5	FE	[redacted]	[redacted]
BASFI CFB	2	FE	[redacted]	[redacted]
ASDAS CFB	2	FE	[redacted]	[redacted]

[a] null effect is 1; [b] null effect is zero. N/A: There was no evidence for secukinumab for this comparison.
Abbreviations: CFB: change from baseline, CrI: credible interval, FE: fixed effect, MD: mean difference, OR: odds ratio.

Quality of life outcomes

The results of the models preferred by the company and the ERG are presented in Table 7. As COAST-W did not report data for ASQoL, the NMA for the outcome only compared tofacitinib to secukinumab. The company only fit unadjusted FE models for both outcomes, due to the sparsity of the studies. CrIs for the estimates for all outcomes included the null effect, therefore there was insufficient evidence to suggest a difference in QoL between tofacitinib and secukinumab and ixekizumab.

Table 7. Results of ERG-preferred unadjusted models for QoL outcomes (bDMARD-experienced patients)

Outcome	Number of Studies	Selected Model	Tofacitinib vs. Secukinumab	Tofacitinib vs. Ixekizumab
			MD (95% CrI)[a]	
ASQoL CFB	4	FE	[redacted]	[redacted]

SF-36v2 PCS CFB	5	FE		[redacted]		[redacted]

[a] null effect is 0. N/A: There was no evidence for ixekizumab for this comparison.

Abbreviations: CFB: change from baseline, CrI: credible interval, FE: fixed effect, MD: mean difference.

Adverse event outcomes

No NMAs of AEs were conducted on a bDMARD-experienced population as there was no subgroup data available based on prior biologic-experience. NMAs on AEs were conducted for mixed population, the results are reported in Section 3.3.

Mixed population

The company included NMAs for efficacy and QoL on a mixed population for the comparison of tofacitinib with adalimumab in the CS. These are not reported here, due to concerns that results for the mixed populations are based mainly on treatment-naïve patients (Section 3.2.3.2). NMAs carried out for AEs in a mixed population are discussed in Section 3.3.3.

3.3 Safety of tofacitinib

3.3.1 Safety evidence in AS and other indications

The CS (page 100) reported that tofacitinib "*has an established safety profile in other indications…*" and that it also "*has a comparable safety profile to adalimumab when evaluating safety during the randomised, placebo-controlled period in an AS population*" (page 88). Although the number of SAEs were low and balanced across groups in the two tofacitinib trials in AS patients, the ERG's clinical advisers alerted the ERG to ongoing concerns about the safety of tofacitinib. The MHRA 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.[1, 19] In addition to the MHRA warning, the U.S. Food and Drug Administration (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.[20] The FDA considers that all JAK inhibitors may pose similar safety risks.

'ORAL Surveillance' randomised safety trial

These warnings came as a result of RCT data showing an increased risk of MACE, malignancies, pulmonary embolism, deep vein thrombosis, VTE, serious infections and all-cause mortality in these at-risk patients. This important safety issue was not mentioned in the company's submission. The study cited by the MHRA was the randomised 'ORAL Surveillance' phase 4 (post-marketing) safety trial comparing tofacitinib (5mg or 10mg) with TNF-alpha inhibitors (etanercept 50mg every week

and adalimumab 40mg every other week) for safety outcomes in 4372 patients with RA, aged 50 years or older with at least one additional cardiovascular risk factor (defined as: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction (MI), cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA, e.g. nodules, Sjögren's syndrome, anaemia of chronic disease, pulmonary manifestations). The co-primary endpoints were non-inferiority of tofacitinib compared to TNF-alpha inhibitors with respect to MACE and malignancies. Patients were followed up for a minimum of three years and the maximum duration of follow-up was six years. Although the trial results have yet to be published in a peer-reviewed journal, they have been posted on the study's clinicaltrials.gov record.[21] Tofacitinib failed to show non-inferiority compared to TNF-alpha inhibitors for both MACE and malignancies with the upper limit of the 95% CI exceeding the non-inferiority margin of 1.8 for both outcomes (hazard ratio (HR) 1.33, 95% CI: 0.91 to 1.94 for MACE and HR 1.48, 95% CI: 1.04 to 2.09 for malignancies). The rates of all-cause mortality were 3.37% for tofacitinib 5mg, 4.53% for tofacitinib 10mg and 2.62% for TNF-alpha inhibitors. The European Medicines Agency (EMA) reported HRs by dose. With tofacitinib 5mg as comparator the results were: MACE, HR 1.24 (95% CI: 0.81 to 1.91); Non-fatal MI HR 2.32 (95% CI: 1.02 to 5.30) and malignancies HR 1.47 (95% CI: 1.00 to 2.18). There were no fatal MIs in patients taking tofacitinib 5mg.[22]

These findings demonstrate the value of conducting a long-term, direct, randomised comparison of treatments on safety outcomes. Prior to this study's results, a study of pooled data from 7061 patients with RA who had received tofacitinib for a median of 3.1 years[23] appeared to show that (with the exception of herpes zoster) rates of tofacitinib safety events were both stable over time and generally similar to biologics.

The ERG asked clarification questions about this issue, including asking for a summary of the tofacitinib safety data relating to the increased risk of the aforementioned SAEs and all-cause mortality, and how they compare with data for TNF-alpha inhibitors. The company responded by stating that analyses of data from PsA, AS, psoriasis and ulcerative colitis populations, as well as in the non-cardiovascular risk RA population, have not shown an increased risk for tofacitinib therapy versus TNF-alpha inhibitors for MACE and malignancy. The ERG notes that most of the data presented by the company focused on differences in incidence rates across diseases, rather than comparisons with TNF-alpha inhibitors. The one study which did compare tofacitinib with TNF-alpha inhibitors was a non-randomised comparison in RA patients which reported similarities in MACE, malignancy, death, and VTE.[24] Given that this study is in RA patients (like the ORAL Surveillance

RCT) and is non-randomised, the ERG does not see this as evidence to allay concerns about the safety of tofacitinib.

The ORAL Surveillance safety trial was conducted in older patients who had at least one additional cardiovascular risk factor. It is uncertain what the safety risks are in younger patients without cardiovascular risk factors. It is also uncertain whether tofacitinib exacerbates pre-existing risk factors for developing the SAEs listed by the MHRA, or is the cause of a new risk factor (or both).

3.3.2 Tofacitinib discontinuation rates

Discontinuation of tofacitinib due to AEs is reported for A3921119 study as [redacted] at 12 weeks follow-up for patients taking 5mg tofacitinib (Table 27 of the CSR). For A3921120 data are reported at 16 weeks and up to 48 weeks follow up as [redacted] and [redacted] respectively for patients taking 5mg tofacitinib (Table 41 of the CSR). No longer-term data on discontinuation due to AEs are available for either clinical trial and therefore, this remains uncertain. Longer term data from an open-label study (ORAL Sequel long-term extension[25]) of tofacitinib (5mg and 10mg) for RA (including 4481 patients followed up to 114 weeks), suggests this could be notably higher, with 28% of patients discontinuing tofacitinib 5mg due to an AE. Furthermore, randomised data from a clinical trial (ORAL surveillance)[21] of tofacitinib (5mg or 10mg) or TNF-alpha inhibitors for RA (including 4372 patients followed up for a minimum of three years and a maximum of 72 weeks) reports permanent discontinuation rates due to AEs of 14.4% for patients taking tofacitinib 5mg and 14.5% for patients taking a TNF-alpha inhibitor (adalimumab or etanercept). Discontinuation due to lack of efficacy is reported only for the A3921120 study at 16 weeks and at 48 weeks follow-up, as [redacted] respectively (Table 14.1.1.2.2 of CSR). Longer-term data on discontinuation due to lack of efficacy are not available.

The ERG also asked the company to comment on the possibility of increased discontinuation rates, and consequent reduction of time on treatment, from the development of risk factors while on treatment with tofacitinib (for example, increased lipid levels or becoming a smoker). The ERG's advisers noted that many AS patients are overweight or obese which predisposes them to MACE and VTE events. The company presented data summarising findings for lipid levels, blood pressure and weight gain in study A3921120, up to 48 weeks follow-up. Of note, after an initial increase in cholesterol levels, these remained stable from week 16 to week 48. Mean blood pressure remained stable throughout the trial and body weight saw a mean increase of 2.2kg at 48 weeks follow-up. The company state there is insufficient data to make conclusion about the annual incidence rate (or similar metric) of acquiring a new risk cardiovascular factor among AS patients initiating tofacitinib, and how this would affect discontinuation rates.

The company also note that results from the NMAs versus adalimumab and secukinumab suggest no statistically significant difference. This analysis reports on a mixed population of bDMARD-experienced and naïve and uses data at 16-week follow-up from the tofacitinib A3921120 trial and adalimumab and secukinumab trials, and 12-week follow-up from the tofacitinib A3921119 trial. For MEASURE trials included in the NMA, longer-term follow-up data are available at 52-104 weeks, although these data are limited and are non-randomised past 16 weeks follow-up. Uncertainty remains around how the longer-term discontinuation rates for tofacitinib compares to other interventions and how this could impact time on treatment.

3.3.3 Network meta-analyses of safety and discontinuation outcomes

In their initial submission, the company did not conduct NMAs on AE outcomes for the comparison of tofacitinib to adalimumab but provided results for these analyses in their response to clarifications. Due to sparse data and the low number of studies in the NMA for SAEs only, an FE model was fit for the outcome. At the clarification stage the company were also asked to conduct an NMA of discontinuation rates due to AEs and SAEs from tofacitinib versus IL-17A inhibitors. Safety NMAs of tofacitinib against secukinumab in a mixed population (including both bDMARD-naïve and -experienced patients) were conducted as none of the included studies reported subgroup data based on prior biologic experience. COAST-W was not included in the networks for safety outcomes, therefore tofacitinib could not be compared to ixekizumab. Previous appraisals of secukinumab (TA407), ixekizumab (TA718) or TNF-alpha inhibitors (TA383) did not conduct safety NMAs.

The company was unable to fit a model for discontinuations due to AEs as all the adalimumab trials had zero discontinuations in the placebo arms. In their response to clarification question A22, the company conducted a frequentist NMA (adding a continuity correction to zero cell studies) which allowed estimation of relative effects for this outcome, although there was a lot of uncertainty in the estimates which are also slightly biased due to the addition of 0.5 to the zero cells. This is another situation where including data on other TNF-alpha inhibitors might have resulted in a more meaningful comparison. The company also fit a baseline-risk adjusted FE NMA model for overall discontinuation.

In their response to clarifications, the company also presented results for NMAs conducted on AE-related discontinuation and SAEs for the comparison of tofacitinib to secukinumab. The ERG agrees with all the models chosen by the company.

Results for the ERG-preferred models are presented in Table 8. CrIs for all the outcomes included the null effect, therefore there was insufficient evidence to suggest a difference in the incidence of AEs and discontinuations between tofacitinib and adalimumab, and tofacitinib and secukinumab. However, the ERG notes that the CrIs are all very wide, indicating large uncertainty in these comparisons.

Table 8. Results of ERG-preferred unadjusted models for AE outcomes (mixed population)

	NMA in Company Submission			NMA in Response to clarifications		
Outcome	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Adalimumab**	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Secukinumab**
			OR (95% CrI)[a]			
Overall discontinuation	5	FE, BL-adj	[redacted]	Outcome not reported in the clarifications response		
AE-related discontinuation	5	FE, BL-adj	[redacted]	5	FE*	[redacted]
SAEs	4	FE	[redacted]	5	FE	[redacted]

[a] null effect is 0, * No RE models fit due to poor convergence

Abbreviations: AE: adverse events, BL-adj: baseline-risk adjusted, CrI: credible interval, FE: fixed effect, NMA: network meta-analysis, OR: odds ratio, RE: random effects-SAE: serious adverse events.

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 tofacitinib to adalimumab and to IL-17A inhibitors (i.e., secukinumab and ixekizumab) for efficacy and QoL outcomes. NMAs were conducted on subgroups based on previous bDMARD-experience. While evidence was available for both bDMARD-naïve and bDMARD-experienced patients for secukinumab, trials for adalimumab were only conducted in bDMARD-naïve patients and the only relevant trial for ixekizumab was conducted in bDMARD-experienced patients. For all efficacy and QoL outcomes, there was no evidence to suggest a difference in effects for tofacitinib compared to adalimumab, 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 ASAS20, ASAS40, and BASDI 50 comparing tofacitinib to secukinumab and ixekizumab. The company fitted several different NMA models but overall, results were similar for all the models explored.

The company did not include all TNF-alpha inhibitors in the network comparing tofacitinib to adalimumab and did not consider fitting a class effect model. Therefore, it is unclear how tofacitinib compares to TNF-alpha inhibitors as a class.

Although the short-term safety and discontinuation data for tofacitinib appear similar to those for adalimumab, long-term safety data for AS patients are not available. Long-term randomised safety trial data from RA patients led the MHRA to issue a safety warning on the use of tofacitinib. The implications of this warning for AS patients means that support for the claim of clinical similarity with bDMARD comparators, in terms of safety, does not appear reasonable.

For AEs and discontinuations, NMAs comparing tofacitinib to adalimumab and secukinumab were conducted on mixed populations and were very uncertain.

4 SUMMARY OF THE ERG'S CRITIQUE OF COST EVIDENCE SUBMITTED

The appropriateness of assessing the cost-effectiveness of tofacitinib in the context of a cost comparison FTA relies on the validity of the assumption of equivalent efficacy (see Section B.3.9.2., CS) and safety (adherence and discontinuation, see Section B.3.10, CS, and response to clarification question 22b) of tofacitinib 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 tofacitinib 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 presented a cost comparison analysis between tofacitinib 5mg twice daily (BID) and adalimumab 40mg Q2W, henceforth referred to as tofacitinib and adalimumab, respectively. After the clarification stage, the company extended the cost comparison to include ixekizumab 80mg every four weeks (Q4W) (henceforth referred to as ixekizumab) and secukinumab 150mg and 300mg per month (secukinumab henceforth refers to secukinumab 150mg monthly, unless stated otherwise) as comparators. The company presented NMA results (response to clarification question A13) to support the assumption of similar efficacy and safety profile of tofacitinib and IL-17A inhibitors (see Section 3.2.3). The company considers adalimumab the most relevant comparator (see Section 2.1).

The costs included in the company's cost comparison are drug acquisition (Section B.4.2.3, CS), administration costs (Section B.4.2.4, CS), and monitoring costs (Section B.4.2.3, CS). Costs are estimated for time horizons of two, five and ten years. The company does not express a preference for any length of time horizon. Costs are reported separately for the first and subsequent years in the model. All costs are expressed in 2019/20 prices and undiscounted. The company considers that tofacitinib 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 costs applied in the cost comparison for the company base case analysis after clarification stage is presented in Table 9. A brief description of the parameterisation and assumptions of the cost comparison are presented in the following sub-sections.

As the company did not present clinical evidence to support the comparison with secukinumab 300mg (See Sections 2.1 and 3.2.3), and did not submit a version of the electronic model parameterised with this dosing schedule, the ERG focusses on the 150mg dosing schedule throughout the cost sections.

Table 9. Summary of costs in the cost comparison analysis

	Tofacitinib	Adalimumab	Ixekizumab	Secukinumab
Dose	5mg BID	40 mg Q2W	160 mg loading, then maintenance 80 mg Q4W	150mg per week for 5 doses, followed by: 150mg per month (secukinumab 150mg), or 300mg per month (secukinumab 300mg).
Mode of administration	Oral	SC injection	SC injection	SC injection
Drug acquisition unit cost	Xeljanz (5mg, 56 tablets): £690.03 (list price), [redacted] (PAS price)	Amgevita (40mg/0.8ml solution for injection, two pre-filled syringes,): £633.60	Taltz 80mg/1ml solution for injection pre-filled pens (pack of 1), £1,125.00 (list price)	Cosentyx 150 mg/1 ml - pre-filled disposable injection (pack of 2), £1,218.78 per pack (list price)
Annual drug acquisition cost	£9,001 (list price) [redacted] (PAS price)	£8,265	Year 1: £15,519 Subsequent years: £14,675	Year 1: £10,234* Subsequent years: £7,949*
Administration cost**	£0	£0	£0	£0
Monitoring costs (quarterly)	1st 12 weeks: £425.81 Subsequent 12 weeks: £82.04	1st 12 weeks: £423.27 Subsequent 12 weeks: £82.04	1st 12 weeks: £423.27 Subsequent 12 weeks: £82.04	1st 12 weeks: £423.27 Subsequent 12 weeks: £82.04

*For the secukinumab 150mg dose; **Originally included in the base case analysis and removed at clarification stage; BID, twice daily; Q2W, every 2 weeks; Q4W, every 4 weeks; PAS, patient access scheme; SC, subcutaneous.

4.1.1.1 Acquisition costs

Acquisition costs for tofacitinib 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.[26] The acquisition cost of adalimumab was based on the BNF 2021 list price of a biosimilar (Amgevita) corresponding to the lowest publicly available price of adalimumab. Biosimilars of adalimumab are available to the NHS at confidential framework prices provided by the Department of Health and Social Care Commercial Medicines Unit (CMU). The company did not present details on the acquisition costs of ixekizumab and secukinumab, but the costs used in the model match those in the BNF 2021.[26] There are also confidential PAS commercial arrangements in place for the use of ixekizumab and secukinumab in the NHS. The drug acquisition costs and results reported in this document do not reflect the framework prices of adalimumab biosimilar or the PAS commercial arrangements for ixekizumab and secukinumab; the PAS prices of ixekizumab and secukinumab are applied in a separate confidential appendix to this report. NICE did not make the confidential framework prices for adalimumab biosimilars available to the ERG; therefore, these could not be considered in the analysis presented in the confidential appendix. The annual and total drug acquisition costs in Table 9 assume the dosing schedules stipulated in the intervention and comparators' SmPCs. The company's analysis did 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 nurse; only the cost of nurse time is included in the analysis, in line with TA383.[27] The unit cost of training corresponds to one hour of nurse time at a general practitioner (GP) practice (with qualifications, £42.00) according to Personal Social Services Research Unit, (PSSRU) 2020,[28] and in line with TA383.[11]

The company removed this cost from their updated base case analysis in response to clinical input provided by the ERG at the clarification stage.

4.1.1.3 Monitoring costs

Monitoring resource use (see Tables 32 and 33, CS, for details) is assumed to be the same for tofacitinib and the comparators, and is sourced from previous appraisals in AS;[2, 12, 27] with the exception of the inclusion of the additional assessment of lipid parameters performed eight weeks following initiation of tofacitinib therapy. 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 12 weeks of treatment) compared to the subsequent maintenance period.

4.1.1.4 Treatment discontinuation rates

Treatment discontinuation was not considered in the company's cost comparison analysis. The ERG requested that the cost-comparison be updated to allow the effect of treatment discontinuation to be explored, but the company declined this request, stating only that rates were similar between tofacitinib and the comparators.

4.1.1.5 Time horizon

The cost comparison did not present results over an explicitly defined time horizon. Instead, the company presented a comparison of costs over the first year of treatment, and a separate comparison of annual costs for any subsequent year. As the analysis did not account for treatment discontinuation, annual costs beyond the first year are constant. In response to a request by the ERG, the company also presented scenarios in which a number of time horizons up to a maximum of 10 years were considered.

4.1.1.6 Assumptions

The key assumptions underlying the cost comparison analysis are listed below:

- Adalimumab is the most relevant comparator in bDMARD-naïve and -experienced patient populations (see Sections 2.1 and 4.2.1); at the ERG request, the company also includes comparisons with ixekizumab and secukinumab.
- Equivalent effectiveness between tofacitinib and comparators means that it is appropriate to evaluate tofacitinib 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 tofacitinib in bDMARD-naïve and -experienced patient population, as no separate analyses are presented by patient population.
- No discontinuation or dose adjustments due to a loss of efficacy or AEs were considered. All patients are assumed to continue to maintenance treatment after the initial response assessment. 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.
- No specific time horizon duration was explicitly assumed, suggesting that differences between tofacitinib and the comparators scale linearly with each additional year due to no assumed discontinuation.

4.1.2 Results

The company presented mean undiscounted annual costs by category of cost for the full population in Table 104 (response to clarification question B3), and for a time horizon of 2, 5 and 10 years in Tables 109 to 111 (response to clarification question B7).

Under the company's assumptions, which include the PAS discount for tofacitinib and using the list prices for the comparators, tofacitinib is less costly than adalimumab, secukinumab and ixekizumab [redacted]. For subsequent years, tofacitinib is less costly than adalimumab, secukinumab and ixekizumab [redacted]. When considering the tofacitinib PAS price, tofacitinib is associated with [redacted] drug acquisition and administration costs, and higher monitoring costs compared to adalimumab, ixekizumab and secukinumab for time horizons of two, five and ten years. Total costs increase for all interventions with the increase of the time horizon.

The company presents a scenario analysis exploring the impact of including the costs of annual lipid monitoring for tofacitinib (Table 102, response to clarification question B2c). Results were not sensitive to the inclusion of this additional cost for tofacitinib, which resulted in an increase of approximately £3 per annum to the total costs of tofacitinib in subsequent years.

Subgroup analyses were considered unnecessary by the company, as the company did not expect differences in costs for tofacitinib and adalimumab in bDMARD-naïve and bDMARD-experienced patients. The only potential cost difference that is highlighted by the company refers to the administration cost of adalimumab for bDMARD-experienced, as patients may not require re-training to self-administer the drug; this cost was dismissed by the company as *"modest"*. Drug administration costs for subcutaneously delivered drugs were removed from the cost comparison at the clarification stage.

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 an error on the dosing schedules of secukinumab and ixekizumab (see Section 4.2.5) in the electronic model submitted by the company at clarification stage, which was corrected. No further errors were detected in the economic model.

The ERG critique focuses on the following aspects of the cost comparison analysis:

- Population, treatment positioning and relevant comparators;
- Adverse events;

- Treatment adherence and discontinuation;
- Time horizon;
- Acquisition costs;
- Monitoring costs;
- Administration costs.

Following the critique, the ERG proposes an alternative base case analysis, exploring alternative assumptions to those used in the company analysis. The results of the ERG preferred base case are presented in a confidential appendix separate to this report.

The ERG notes that the cost-comparison model does not formally model response assessment at the end of the trial period, and therefore, costs are not estimated separately for patients who do not have a response to treatment at this time point, and move to the next line of treatment. Therefore, the differential costs between responders and non-responders to each of the comparators are not captured in the cost comparison model. This is a limitation of this analysis, but the ERG does not consider it to affect conclusions.

4.2.1 Population, treatment positioning and relevant comparators

The company positions tofacitinib 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 adalimumab to be the most relevant comparator.

As detailed in Section 2.1, the ERG considers adalimumab is unlikely to be a relevant comparator for the cost comparison analysis; secukinumab is likely to be the most relevant comparator for bDMARD-experienced patients.

If tofacitinib 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 therefore 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.

Another issue raised in Section 2.1 is that the population in which the clinical evidence provided by the company (critiqued in Section 3) was generated is wider than the population who will be eligible for treatment with tofacitinib in the UK according to the MHRA safety warning[1] and for the purpose of this appraisal. This introduces additional uncertainty around the equivalence assumption which underpins the appropriateness of the cost comparison.

The assumption of equivalent effectiveness and safety profile of tofacitinib and comparators is also particularly uncertain in the bDMARD-experienced population because the majority of patients treated with tofacitinib in clinical trials have not been previously treated with bDMARDs (Section 3.2.3).

4.2.2 Adverse events

As detailed in Sections 2.1 and 3.3, the ERG is concerned that the safety profile of tofacitinib is 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,[1, 19, 20], sparsity of long-term safety data, and concerns expressed by clinical advisers to the ERG.

At the 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 support the existence of differences between tofacitinib and bDMARDs. In brief, the ERG critique of the evidence presented concludes it is insufficient to establish the equivalence of tofacitinib compared to bDMARDs, especially in terms of long-term safety (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 tofacitinib and adalimumab (as well as with IL-17A inhibitors) cannot be fully dealt with within the boundaries of a cost comparison FTA, and requires a full cost-effectiveness analysis to capture the impact on HRQoL due to the AEs and the consequences of discontinuing treatment (and switching to subsequent ones).

4.2.3 Treatment adherence and discontinuation

The company declined to present analyses considering the effect of treatment discontinuation upon ERG request, stating only that the discontinuation rates of tofacitinib and the three comparators in the NMAs were similar (see Section 3.2.3.4).

At present, the cost comparison can only provide the total costs per patient actively receiving treatment, rather than the ongoing costs of an average patient initiating treatment at the outset of the model. The consideration of discontinuation would have some informative value in a cost comparison context. Namely, it would allow internally consistent estimates of budget impact associated with tofacitinib across the population. That is, accounting for discontinuation would allow time on treatment to be explicitly modelled, which would inform an appropriate time horizon over which to

measure differences in accrued costs. The analysis would therefore give a more representative impression of the mean total costs of treatment and their magnitude relative to monitoring costs over time. However, estimates of real-world discontinuation rates remain themselves subject to uncertainty. As discussed in Section 4.2.4, additional monitoring costs associated with tofacitinib will accrue over the course of a typical patient's time on treatment. To understand the differences in monitoring costs between tofacitinib and the comparators, we must consider both the proportion of patients remaining on treatment and the timescales over which they are treated.

The ERG considers there to be a non-negligible risk that the long-term rates of treatment discontinuation experienced on tofacitinib will not be comparable to the chosen comparators. For the reasons discussed in Section 2.1, the restrictions issued by the MHRA may lead to additional sources of discontinuation relating to the development of risk factors for MACE, VTE, and malignancy, which were not captured in the syntheses of treatment discontinuation in the short-term. Discontinuation relating to shorter duration of treatment effect (i.e., potential loss of treatment effect) compared to bDMARDs has also not been adequately explored in the presented analyses. Therefore, there remains significant uncertainty regarding long-term discontinuation that cannot be captured in a cost comparison analysis. For example, in the event that discontinuation rates are indeed higher on tofacitinib, the cost comparison analysis is unable to characterise the impact on HRQoL and the cost of moving to a subsequent line of therapy.

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 presented the results of sensitivity analyses using time horizons of two, five, and ten years. As treatment discontinuation was not considered in the updated model, the costs accrued annually do not change after the first year. The effect of increasing the time horizon is therefore illustrative only of budget impact per patient remaining on treatment.

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 tofacitinib (See Section 4.2.6) 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 (see Section 4.2.6). The ERG therefore considers the most relevant time horizon to 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.

4.2.5 Acquisition costs

The cost comparison model estimates acquisition costs in the first and subsequent years for tofacitinib and comparators. In the updated model submitted at the clarification stage by the company, the number of secukinumab doses at first and subsequent years was not calculated appropriately as it was assumed that this drug was administered in the maintenance period once every four weeks in contrast to once a month as per the dosing schedule recommended in the BNF.[26] Furthermore, the company also underestimated the number of doses administered for ixekizumab in the first year, by considering a longer interval between the initial loading dose and subsequent doses compared to what is recommended in the BNF (5 vs. 4 weeks).[26] The ERG corrected the dosing schedules for the IL-17A comparators in what is henceforth referred to as the ERG revised model; these are shown in Table 10 alongside those estimated by the company. The ERG preferred base case analysis applies the resource use described for the ERG revised model.

Table 10. Dosing schedules of secukinumab and ixekizumab in the models

Number of doses	Company's model*		ERG revised model*,**	
	1st year	Subsequent years	1st year	Subsequent years
Secukinumab	16.79	13.04	16.08	12.00
Ixekizumab	13.79	13.04	15.04	13.04

*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

Prior to clarification, the company had assumed the year had a 365 days duration for the purpose of calculating acquisition costs of interventions in the cost-comparison. This was corrected at clarification stage to reflect that on average a year has a 365.25 days duration.

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.[29] The company reported the version of the NHS reference costs[30] used in response to clarification questions, but updated the model in accordance to the source used by the ERG. The ERG notes 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 12 (Appendix 2); these estimates also include other corrections detailed in Appendix 2. These corrections do not impact the results, as they apply to tofacitinib and comparators equally (with the exception of the baseline lipid profile assessment included for tofacitinib but not to comparators).

The ERG requested at the clarification stage that further monitoring costs were considered for patients treated with tofacitinib, namely a baseline risk assessment including lipid profiling, blood pressure

measurement, body weight measurement, and diabetes tests, and further annual lipid profile monitoring. The company stated that regular monitoring of cardiovascular risk factors is recommended for all patients with AS,[31] therefore it would affect both arms of the cost-comparison equally (response to clarification questions B1-2). A scenario analysis adding the cost of annual lipid profile monitoring (see Section 4.1.2, was presented to address this concern (Table 102, response to clarification question B2c), but it had a negligible impact on results.

The ERG notes that clinical guidance on monitoring cardiovascular risk factors in patients with AS predates the MHRA safety warning on tofacitinib.[1] Therefore, it is likely that the additional ongoing monitoring costs of tofacitinib, given the safety concerns, are not fully reflected in the model. Furthermore, there may be clinical variation on the level of additional resource use associated with monitoring patients on treatment with tofacitinib in light of safety concerns highlighted in Sections 2.1 and 3.3, so this represents an area of uncertainty. The costs associated with this will be accrued while patients are on treatment and, therefore, it is important that the time horizon of the cost-comparison covers the expected treatment duration. In the ERG preferred base case, annual lipid profile monitoring is included in the monitoring costs of tofacitinib, as a proxy for cardiovascular risk factors monitoring. The ERG notes that this is a small cost (£2.53 per year), and may not be reflective of costs to the NHS.

4.2.7 Administration costs

As previously discussed in Sections 2.1 and 4.2.1 the ERG considers tofacitinib to be most appropriately positioned in bDMARD-experienced patients. As such, the majority of patients initiating treatment on one of the comparator therapies will have already received training in the use of self-injecting SC administration devices at previous lines of therapy. Moreover, many companies provide this training free of cost to the NHS – particularly in the case of originator agents (e.g. Cosentyx and Taltz). Therefore, the ERG considers it appropriate that this cost is removed from the base case. The company agreed with the ERG's position and removed the one-off training cost from their updated 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 (see Table 103 and 104, response to clarification question B3); it differs from the company's by incorporating the following set of assumptions:

1. Monitoring of patients on treatment with tofacitinib requires baseline and annual lipid profile assessment in addition to the monitoring resource use associated with the comparators (see Section 4.2.6);

2. The unit cost of a TB test corresponds to £66.23 (see Section 4.2.6);
3. Dosing schedules of ixekizumab and secukinumab have been adjusted as described in Section 4.2.5.

Results of the base case analysis for the first and subsequent years, and for time horizons ranging from two to ten years, are presented in the confidential appendix to this report.

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 comparing tofacitinib to adalimumab and secukinumab in bDMARD-naïve populations and to secukinumab and ixekizumab in bDMARD-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 detected.
- The company updated the model at 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:

- An important MHRA safety warning exists for tofacitinib. It is based on randomised safety trial evidence showing that patients on tofacitinib who have common cardiovascular and malignancy risk factors have an increased risk of MACE, malignancies, pulmonary embolism, deep vein thrombosis, VTE, serious infections and all-cause mortality. This means the assumption of safety equivalence is not reasonable.
- Considering the MHRA guidance on restricted use and tofacitinib's SmPC, the ERG estimates that at least half of the AS patients eligible for tofacitinib should only receive it if there are no suitable treatment alternatives, i.e. as a last line of therapy.

- Given these safety issues, the appropriate comparator for most patients would be established clinical management without biologics, though this is not listed in the NICE scope. 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.
- Tofacitinib could be considered as a new line of therapy.
- 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 severely needle-phobic.
- Networks of evidence were sparse and did not include all TNF-alpha inhibitors, therefore it is unclear how tofacitinib compares to TNF-alpha inhibitors as a class.
- Relative effect estimates comparing tofacitinib to secukinumab and ixekizumab are uncertain.
- The assumption of equivalent efficacy and safety (adherence and discontinuation) between tofacitinib and the included comparators is highly uncertain. The sparsity of safety evidence on the use of tofacitinib in a bDMARD-experienced population is of particular concern.

5.2.2 Economic evidence:

- The appropriateness of assessing the cost-effectiveness of tofacitinib 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, particularly for longer-term AEs, from the cost comparison is an important area of uncertainty. If the safety profile of tofacitinib is worse than that of comparators, this exclusion would favour tofacitinib in the cost-comparison under consideration. Differences in the safety profile between interventions 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.
- Treatment discontinuation has not been formally modelled, and long-term discontinuation due to AEs or loss of tolerance is highly uncertain. Not accounting for treatment discontinuation introduces uncertainty on the costs of tofacitinib and comparators over time, and may impact on downstream costs and HRQoL outcomes.

- The relevant time horizon for the cost comparison analysis is uncertain, the ERG and company's base case results are sensitive to this parameter once the confidential prices of the comparators are considered.
- Costs associated with monitoring patients on treatment with tofacitinib are uncertain and are likely to be higher than what was considered in the cost comparison model, given safety concerns

on the use of this treatment raised by the MHRA. This uncertainty in the incremental monitoring costs associated with tofacitinib is further amplified by uncertainties surrounding treatment discontinuation and time horizon duration, as the proportion of patients who would remain on treatment with tofacitinib over time is unknown.

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APPENDICES

APPENDIX 1: INCLUDED STUDIES

Table 11. Studies included in NMAs of each outcome for bDMARD-naïve and bDMARD-experienced populations

Outcomes	bDMARD-naïve‡			bDMARD-experienced		
	Tofacitinib	Adalimumab	Secukinumab	Tofacitinib	Secukinumab	Ixekizumab
ASAS20	A3921119 A3921120[a]	ATLAS COAST-V Huang 2014 M03-606	MEASURE 2 [a] MEASURE 4 [a] MEASURE 5 [a]	A3921120 [b]	MEASURE 2 [b] MEASURE 4 [b] MEASURE 5 [b]	COAST-W
ASAS40	A3921119 A3921120 [a]	ATLAS COAST-V Huang 2014 M03-606	MEASURE 2 [a] MEASURE 4 [a] MEASURE 5 [a]	A3921120 [b]	MEASURE 2 [b] MEASURE 4 [b] MEASURE 5 [b]	COAST-W
BASDAI50	A3921119 A3921120 [a]	COAST-V Huang 2014	---	A3921120 [b]	---	COAST-W
BASDAI CFB	A3921119† A3921120†	ATLAS COAST-V Huang 2014 M03-606	MEASURE 2 [a, c] MEASURE 4 [a, c] MEASURE 5 [a, c]	A3921120 [b]	MEASURE 2 [b] MEASURE 4 [b] MEASURE 5 [b]	COAST W
BASFI CFB	A3921119 A3921120 [a]	ATLAS COAST-V M03-606	---	A3921120 [b]	--	COAST-W
BASMI CFB	A3921119 A3921120 [a]	ATLAS Huang 2014 M03-606	---	---	--	--
ASDAS	---	---	---	A3921120 [b]	--	COAST-W
ASQoL CFB	A3921119 A3921120 [a]	ATLAS	MEASURE 2 [a, c] MEASURE 4 [a, c] MEASURE 5 [a, c]	A3921120 [b]	MEASURE 2 [b] MEASURE 4 [b] MEASURE 5 [b]	---
SF-36v2 PCS CFB	A3921119 A3921120 [a]	ATLAS COAST-V Huang 2014	MEASURE 2 [a, c] MEASURE 4 [a, c] MEASURE 5 [a, c]	A3921120 [b]	MEASURE 2 [b] MEASURE 4 [b] MEASURE 5 [b]	COAST-W
SF-36v2 MCS CFB	A3921119 A3921120 [a]	ATLAS Huang 2014	---	---	---	---

[a] Subgroups of bDMARD-naïve patients from the study were used for the NMA. [b] Subgroups of bDMARD-experienced patients from the study were used for the NMA. [c] Sulfasalazine was treated as a placebo in the NMA. ‡ NMAs for the bDMARD-naïve were conducted in two separate analyses: tofacitinib vs. adalimumab and tofacitinib vs. secukinumab.

†There appeared to be a discrepancy in Table 44 of the clarification response, where it says that there were 102 patients in the tofacitinib arm and 105 patients in the placebo arm. The ERG assumes that the patient population (N) in trials A392119 and A3921120 were swapped, but it was unclear whether this was a typographical error or an error that was carried into the NMAs. The ERG was not able to check this in the files provided by the company in their clarification response.

APPENDIX 2: UPDATED MONITORING COSTS

In addition to updating the unit cost in accordance with the version identified by the ERG [NHS reference cost 2019/20], at clarification stage the company also 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 for latent TB detection. The company replaced the cost of the Heaf test with that of an IGRA test, the QuantiFERON – TB Gold-In Tube (QFT-GIT), and sourced it from a recent HTA report.[32] The ERG notes that according to the ERG clinical advisers there is one other test used in clinical practice, the T-SPOT.TB. 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[33] used in the HTA report[32] uprated from 2009/10 to 2019/20 prices.[28]

The unit costs for antinuclear antibody testing and double stranded deoxyribonucleic acid (DNA) tests was also corrected to that of currency code DAPS06 (Other currencies),[29] which reflects the costs of an immunological assay.

Table 12. Monitoring unit costs in the ERG revised model

Item	Unit cost	Source
Full blood count	£2.53	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS05 - haematology).[29]
Erythrocyte sedimentation rate	£2.53	
Liver function test	£1.20	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS04 – clinical biochemistry).[29]
Urea and electrolytes	£1.20	
Chest X-Ray	£32.72	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Direct access plain film (Currency code DAPF).[29]
Tuberculosis test	£66.23	Pareek et al. (2013)[33] 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.[28]
Antinuclear antibody	£7.40	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS06 - immunology).[29]
Double-stranded DNA test	£7.40	
Specialist visit	£149.14*	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Consultant-led non-admitted face-to-face attendance, follow-up. (Currency code WF01A).[29]
Lipid parameters	£2.53	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS05 - haematology).[29]

*Unit cost for Rheumatology visit; DNA, deoxyribonucleic acid; HCHS, hospital & community health services; NHS, National Health Service; NHSCII, NHS cost inflation index; PSSRU, Personal Social Services Research Unit.