NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for previously treated moderate active rheumatoid arthritis [ID3878]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Upadacitinib for previously treated moderate active rheumatoid arthritis [ID3878]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document** from **AbbVie**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. National Rheumatoid Arthritis Society
   b. British Society for Rheumatology (RCP endorse BSR comments)
   c. UCB Pharma Ltd

4. **Evidence Review Group critique of company comments on the ACD** prepared by Peninsula Technology Assessment Group

5. **AbbVie final response to model discrepancy**

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1		British Society for Rheumatology	The BSR welcomes the opportunity to respond to the ACD on **Upadacitinib for treating moderate rheumatoid arthritis.** We are disappointed that the committee considered that upadacitinib could not be used to treat moderate RA. We feel that the committee may have made inappropriate assumptions in reaching this conclusion. We address our concerns below.	Thank you for your comment.
2		British Society for Rheumatology	NICE Guideline NG 100 recommends that patients with rheumatoid arthritis (RA) should be treated to a target of remission or low disease activity in all patients. In those who fail conventional synthetic disease modifying anti-rheumatoid drugs (csDMARDs) and have persistent moderate disease with a DAS28 >3.2 and ≤ 5.1, there are limited therapeutic options. Currently only filgotinib is currently approved by NICE for these patients. However, patients with persistent moderate disease have increasing disability from observations in several studies: • Conaghan and colleagues (Conaghan PG et al *Rheumatology* 2010;49:1894–1899) found that even over a 6 month period, up to 25% of those with moderate disease had progressive disability. • The Early Rheumatoid Arthritis Study (ERAS)(Jayakumar K et al *Rheumatology* 2012;51:169-75) is a multicentre inception cohort which recruited 1,465 patients with early RA (<2 years disease duration, no prior csDMARD) between 1986 and 1999 from nine hospitals in England, followed yearly for up to 25 years (median follow-up 10 years). The dataset recorded HAQ values of patients at baseline, 6 months, and yearly from year 1 to year 15. We commissioned a detailed analysis of the database. We analysed patients who would be eligible for a biologic drug from TA375 compared with those with persistently moderate disease (patients who had failed methotrexate or at least two non-methotrexate DMARDs or at least one combination DMARD). For those patients who received a TNF inhibitor during the study, only data up to the year prior to the prescription of the TNFi was included in the analysis. There were 868 patients who had a mean DAS28 in the moderate range (119 patients of these patients had a DAS28 that was never >5.1 - 13% of those not in low disease state or remission). In the whole ERAS dataset, 602 patients had high HAQ progression, defined as an annual progression rate ≥0.06. Of these 602 patients, 319 (53%) had moderate RA with a mean DAS28 ≥3.2 and ≤5.1. Therefore approximately a third	Comment noted. The Final Appraisal Document (FAD) recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs.

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			(36.8%) of all moderate patients had high HAQ progression. • In the Early Rheumatoid Arthritis Network (ERAN) study, Kiely and colleagues (Kiely P et al *Rheumatology* 2011;50:926–31) found that only 52% of 170 patients with moderate disease achieved a Health Assessment Questionnaire score (HAQ) < 1.25 after 2 years despite csDMARDs, compared with 79% of 161 patients who had low disease activity or remission. • In a further analysis of the ERAS and ERAN database, Nikiphorou and colleagues (Nikiphorou E et al *Ann Rheum Dis* 2016;75:2080–2086) found significant progression over time of HAQ independent of whether the DAS score was at the higher or lower part of the moderate range. However, those in the higher range required more orthopaedic surgery. • A recent meta-analysis of 'moderate' RA by Edwards and colleagues (Edwards CJ et al *Rheumatol Adv Pract*. 2019;3:rkz002) concluded that certain factors predicted a worse radiographic, DAS or functional outcome including a DAS towards the upper moderate range and CCP positivity.	
3		British Society for Rheumatology	We note that when modelling updacitinib after failure of a single csDMARD that the ICER exceeds £30,000/QALY compared with modelling after failure of two csDMARDs. We agree with the committee that it is inappropriate to consider advanced therapies unless there has been failure of two csDMARDs. We would support the use of advanced therapies including upadacitinib at that stage.	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs.
4		British Society for Rheumatology	We also agree with the committee that Best Supportive Care is the most appropriate comparator but disagree fundamentally with the ERG that this equates to the placebo response in the SELECT trials. Entry criteria to SELECT-NEXT only required failure of a single csDMARD. It is established that patients have a poor response to other csDMARDs if they have failure of more than one csDMARD. These trials were undertaken with a novel and innovative compound. When entering the study, patients would have had high expectation of a response - reflected in the placebo response. This is in contrast to BSC where a patient is informed that they will remain on a csDMARD that has failed. It cannot be appropriate to then equate the placebo response to BSC. To our knowledge this approach has not been undertaken in previous appraisals in rheumatoid arthritis and we are concerned that this is not a fair assessment.	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs.
5		British Society for Rheumatology	We also have concerns regarding the ERG and committee's understanding of disease progression. The disease activity in an individual with rheumatoid arthritis without treatment tends to persist with a similar degree of disease activity over time. The DAS is a composite score to reflect disease activity. It is not a measure of disability. Patients with moderate DAS have progression in disability and joint damage measured by HAQ and similar parameters (as discussed above) yet	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs.

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			remain with a moderate DAS. Only a minority will develop an increase in active synovitis over time reflected by an increase in DAS that may then exceed 5.1 and be labelled as severe. We note that in the ERAN database the committee agreed that 19% of patients increase DAS score from a moderate to a severe range. There is no evidence that a significantly larger number of patients will do so over a longer period of time. Our analysis of the ERAS database does not also suggest that this is a common outcome. We are concerned that the committee may have been misled by the uncertainty of this aspect.	
6		British Society for Rheumatology	We have a major concern regarding the committee's decision to have a threshold of £20,000/QALY. We believe the committee could be accused of acting unfairly in the way they have interpreted NICE's guide to methods of technology appraisal. Upadacitinib is an innovative compound. It therefore falls into the category where it can be approved if an ICER falls between £20,000 to £30,000 range. The methods state: *6.3.3 Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors:* *The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.* *Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained.* *The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure.* *The technology meets the criteria for special consideration as a 'life-extending treatment at the end of life' (see section 6.2.10)* *Aspects that relate to non-health objectives of the NHS (see sections 6.2.20 and 6.2.21).*	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs. See section 3.16 of the FAD for a summary of the committee's revised assumptions.
7		British Society for Rheumatology	The Methods do not state that the committee may prefer to adopt an ICER threshold of £20,000/QALY for an innovative technology because of uncertainty. However, in the ACD the committee state: '*Because of this uncertainty, the committee agreed that an acceptable ICER would be around £20,000 per QALY gained.'* We consider this to breach fairness of the process. We also disagree with the grounds of the uncertainty as discussed above. We have reviewed the ICERs from the company's submission and do not agree that the uncertainty would plausibly increase the ICER above £30,000 – the threshold used by NICE for innovative technologies in rheumatoid arthritis for the past fifteen years.	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs. See section 3.16 of the FAD for a summary of the committee's revised assumptions.
8		British Society for	We consider that the development of Janus kinase inhibitors is a major step in the	Comment noted. The FAD recommends upadacitinib

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		Rheumatology	management of rheumatoid arthritis. It is important that clinician's may have a choice of technologies for managing rheumatoid arthritis and this applies to patients with moderate DAS as well as those with more active disease. We hope the committee will review their decidion and approve upadacitinib for these patients.	with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs.
9		National Rheumatoid Arthritis Society	As a patient organisation we would of course like to see the availability of the most efficacious therapeutics for people living with rheumatoid arthritis who are in moderate disease activity who, in the opinion of their rheumatologists, would benefit from treatment with such agents. And from the work we have done as an organisation, we are very aware of the enormous, and potentially preventable, suffering that many of our members have as a consequence of denial of access to effective drugs. In light of these remarks, we are disappointed with the recommendations from NICE in the ACD for upadacitinib in moderate disease activity in rheumatoid arthritis. We have two specific points to raise. We note that NICE have indicated that the cost effectiveness of upadacitinib exceeds an arbitrary threshold of £20,000 cost per QALY. And yet our understanding is that in all previous NICE appraisals, the threshold has been (arbitrarily) set at £30,000. Why have NICE made this change?	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs. See section 3.16 of the FAD for a summary of the committee's revised assumptions.
10		National Rheumatoid Arthritis Society	We recognise that health economic modelling is complex and that there is a wide variability in many of the parameters that have to be employed in the model such that the confidence intervals of the estimate of cost effectiveness are wide and may even lack credibility. In the case of this modelling, the use of placebo response data from the RA-Next trial is one such parameter that can legitimately be questioned given that the data reflects mean placebo response rates in an internationally recruited trial when it is well know that there is huge geographical heterogeneity in the context of trials and real world clinical practice. We are not therefore persuaded that the modelling is representative of the UK patient situation although we acknowledge the challenges in arriving at a robust and credible estimate of cost-effectiveness as it applies to the UK population.	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs.
11		AbbVie	**NICE have reaffirmed the appropriateness of the approach taken in TA375 and set a clear precedent for modelling the moderate RA pathway** Through the partial review of TA375, NICE has recommended the use of adalimumab, infliximab, and etanercept for moderate RA patients. The Committee considered the most appropriate treatment sequences and efficacy assumptions to be the same as we have advocated for in this appraisal, which are aligned to the original TA375 assumptions and the	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs. See section 3.16 of the FAD for a summary of the committee's revised assumptions.

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>subsequent appraisals of baricitinib [TA466], tofacitinib [TA480], and sarilumab [TA485] (see Table 1). In all cases, the assumptions in table 1 were included in the base case models that informed decision-making and therefore considered the most appropriate method of modelling the moderate RA pathway.

The approach taken in the appraisal of upadacitinib in moderate RA clearly deviates from this precedent and falls short of the standards of predictability, transparency, and consistency that NICE is bound by. In AbbVie's view, the validation of the established approach in moderate RA through the partial review of TA375 and, at the same time, the introduction of a significant change in that same approach through the appraisal of upadacitinib, without robust justification or clear support from clinical experts, seriously undermines the fairness of the upadacitinib appraisal.

We ask the Committee to consistently apply the clinically validated treatment sequences that have been set as the clear precedent for RA appraisals.

<u>Table 1. Assumptions used to inform decision-making in partial review of TA375</u>
<table><tr><th>Treatment arm</th><th>First treatment for moderate disease</th><th>Second treatment for moderate disease</th><th>Third treatment for moderate disease</th><th>First treatment for severe disease</th><th>Second treatment for severe disease</th><th>Third treatment for severe disease</th></tr><tr><td>Treatment</td><td>Biological DMARD</td><td>Methotrexate
45.2% efficacy</td><td>Conventional DMARDs
0% efficacy</td><td>Adalimumab (infliximab if adalimumab is used in moderate disease)</td><td>Rituximab</td><td>Tocilizumab</td></tr><tr><td>Comparator</td><td>Methotrexate
45.2% efficacy</td><td>Conventional DMARDs
0% efficacy</td><td>-</td><td>Adalimumab</td><td>Rituximab</td><td>Tocilizumab</td></tr></table>Abbreviations: DMARDs, disease-modifying antirheumatic drugs.</td><td></td></tr>
<tr><td>12</td><td></td><td>AbbVie</td><td></td><td>Comment noted. The FAD recommends upadacitinib</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			NICE should apply the £30k per QALY threshold to inform decision-making Since the commencement of this appraisal, four treatments have now been recommended in moderate RA, thereby considerably reducing the uncertainty in this indication. We would ask for consistency with the partial review of TA375, where the Appraisal Committee deemed it appropriate to recommend technologies using the £30k per QALY threshold to inform decision-making.	with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs. See section 3.16 of the FAD for a summary of the committee's revised assumptions.
13		AbbVie	**Using the placebo arm of the SELECT-NEXT trial to model the efficacy of best supportive care is not appropriate** AbbVie does not think that it is appropriate to apply a treatment response to BSC in the comparator arm only to account for an assumed placebo response seen in clinical trials. This is in direct conflict to precedent, where csDMARD efficacy assumptions are taken from network meta-analyses, and is problematic for the following reasons: • Applying a treatment response to BSC fundamentally contradicts the committee's determination that csDMARDs given as BSC is not associated with a EULAR response. • Applying a treatment response to BSC to only account for placebo effect would suggest patients would be given a placebo pill to yield this response, which does not happen in clinical practice. The base-case should revert to the treatment sequences and efficacy assumptions that are consistent with the clear precedent set down by the partial review of TA375, as detailed in the previous section.	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs. See section 3.16 of the FAD for a summary of the committee's revised assumptions.
14		AbbVie	**The rate of progression from moderate to severe disease does not contribute to uncertainty in the cost effectiveness of upadacitinib** AbbVie remains confident in the validity of the base case estimate but accepts the ERG preferred scenario to model the progression of patients from moderate to severe disease. Importantly, sensitivity analysis conducted by AbbVie demonstrated that varying the rate of progression only had a small impact on the ICERs and does not lead to any meaningful uncertainty in cost-effectiveness. This has been confirmed by the independent sensitivity analysis conducted by the	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs. See section 3.16 of the FAD for a summary of the committee's revised assumptions.

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			Assessment Group for the partial review of TA375, which reached the same conclusion.	
15		AbbVie	**<u>The preferred treatment sequence for people whose disease progresses from moderate to severe disease is the most appropriate for decision-making</u>** AbbVie believes the treatment sequences in the preferred scenario for severe disease are the most appropriate for decision-making. The accepted approach in all other RA appraisals has been to position an IL-6 third line in severe disease and so does not contribute to uncertainty in the cost-effectiveness of upadacitinib. During the partial review of TA375, the Assessment Group model was updated to reflect that patients access biologic therapies when their disease progresses to severe RA. This led to the update of the treatment sequences in the base case of the Assessment Group model and positioned tocilizumab third line without any discussion of alternative scenarios. Based on this clear precedent, it would be inappropriate to consider alternative scenarios that included anything other than an IL-6 third line in severe disease. Should the Appraisal Committee feel it necessary to align with precedent, tocilizumab could be inserted instead of sarilumab.	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs. See section 3.16 of the FAD for a summary of the committee's revised assumptions.
16		UCB Pharma	Issue statement "the ERG and company considered that the safety profile for upadacitinib is similar to other biological DMARDs". UCB considers the above statement misleading because it does not represent available evidence. Upadacitinib and other JAK inhibitors are not biologic DMARDs (bDMARDs), they are targeted synthetic DMARDs (tsDMARDs). Adverse events from the SELECT-COMPARE trial were numerically higher for upadacitinib than adalimumab, in most cases. The FDA and EMA both issue an additional box warning for upadacitinib and other JAK inhibitors for venous thromboembolism risk, this is not the case with adalimumab or other bDMARDs. Therefore, it is inappropriate to conclude that upadacitinib's safety profile is similar to biological DMARDs.	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs.
17		Web comment	We acknowledge that the appraisal document is currently negative, but we would like to feedback on the proposed entry criteria should the recommendation change to a positive recommendation after consultation. Eligibility criteria for treatment with biologic agents for patients with moderate disease need to be consistent across all TAs for this cohort of patients to ensure that appropriate, safe patient pathways can be developed. Technology appraisal guidance [TA676] Filgotinib for treating moderate to severe	Comment noted. The FAD recommends upadacitinib with methotrexate or upadacitinib alone as a treatment option for moderate RA that has responded inadequately to intensive therapy with after 2 or more conventional DMARDs.

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			rheumatoid arthritis states: 'Filgotinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with 2 or more conventional disease-modifying antirheumatic drugs (DMARDs)' The eligibility criteria stated for upadacitinib in this appraisal document defines a cohort of patients: who cannot tolerate, or whose disease has responded inadequately to, 1 or more conventional disease-modifying antirheumatic drugs (DMARDs).' One TA requiring a patient to have tried one DMARD without any specific reference to methotrexate, and another requiring that the patient has had two DMARDs including methotrexate unless it is contraindicated or if people cannot tolerate it, makes no sense in the context of current or future management pathways. If the efficacy and tolerability of methotrexate is not trialled in all patients, unless contraindicated, prior to initiation of upadacitinib, they will essentially be required to take a step back in the pathway to trial methotrexate prior to being eligible for treatment with other JAKs or biologics, should their treatment fail. If the recommendation changes after the consultation and the drug is to be approved for this cohort or patients, the initiation criteria should reflect those specified in other TAs for moderate disease. There also needs to be clarity on this being an alternate JAK option based on co-morbidites rather than an additional treatment option as another step in the pathway. Inevitably a significant proportion of these patients will move down the pathway and if these options are being used early, we could end up with patients with severe disease who have run out of treatment options. The recommendations of this individual TA need to be taken in context of the whole patient treatment pathway, and not make recommendations in isolation which are then problematic to implement. We also have more general concerns about the safety aspects of a positive recommendation. Conventional DMARDs have a long history of effectiveness whereas JAKs are relatively new, and therefore opening up access to a significantly larger population does not seem clinically appropriate. In addition, lowering the threshold for initiation on a JAK could significantly extend the cohort of RA patients eligible to move further along the RA treatment pathway without fully exploring conventional therapies which are safely delivered in Primary Care. This will potentially put additional pressure on secondary care rheumatology teams.	

NICE National Institute for Health and Care Excellence

Upadacitinib for previously treated moderate active rheumatoid arthritis [ID3878]

Consultation on the appraisal consultation document – deadline for comments **5pm on 28 May 2021..** Email: NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AbbVie
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**NICE have reaffirmed the appropriateness of the approach taken in TA375 and set a clear precedent for modelling the moderate RA pathway** Through the partial review of TA375, NICE has recommended the use of adalimumab, infliximab, and etanercept for moderate RA patients. The Committee considered the most appropriate treatment sequences and efficacy assumptions to be the same as we have advocated for in this appraisal, which are aligned to the original TA375 assumptions and the subsequent appraisals of baricitinib [TA466], tofacitinib [TA480], and sarilumab [TA485] (see Table 1). In all cases, the assumptions in table 1 were included in the base case models that informed decision-making and therefore considered the most appropriate method of modelling the moderate RA pathway. The approach taken in the appraisal of upadacitinib in moderate RA clearly deviates from this precedent and falls short of the standards of predictability, transparency, and consistency that NICE is bound by. In AbbVie's view, the validation of the established approach in moderate RA through the partial review of TA375 and, at the same time, the introduction of a significant change in that same approach through the appraisal of upadacitinib, without robust justification or clear support from clinical experts, seriously undermines the fairness of the upadacitinib appraisal. We ask the Committee to consistently apply the clinically validated treatment sequences that have been set as the clear precedent for RA appraisals. **Table 1. Assumptions used to inform decision-making in partial review of TA375** **Treatment arm** / **First treatment for moderate disease** / **Second treatment for moderate disease** / **Third treatment for moderate disease** / **First treatment for severe disease** / **Second treatment for severe disease** / **Third treatment for severe disease** Treatment / Biological DMARD / Methotrexate 45.2% efficacy / Conventional DMARDs 0% efficacy / Adalimumab (infliximab if adalimumab is used in moderate disease) / Rituximab / Tocilizumab Comparator / Methotrexate 45.2% efficacy / Conventional DMARDs 0% efficacy / - / Adalimumab / Rituximab / Tocilizumab Abbreviations: DMARDs, disease-modifying antirheumatic drugs.
2	**NICE should apply the £30k per QALY threshold to inform decision-making** Since the commencement of this appraisal, four treatments have now been recommended in moderate RA, thereby considerably reducing the uncertainty in this indication. We would ask for consistency with the partial review of TA375, where the Appraisal Committee deemed it appropriate to recommend technologies using the £30k per QALY threshold to inform decision-making.

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3	**Using the placebo arm of the SELECT-NEXT trial to model the efficacy of best supportive care is not appropriate** AbbVie does not think that it is appropriate to apply a treatment response to BSC in the comparator arm only to account for an assumed placebo response seen in clinical trials. This is in direct conflict to precedent, where csDMARD efficacy assumptions are taken from network meta-analyses, and is problematic for the following reasons: • Applying a treatment response to BSC fundamentally contradicts the committee's determination that csDMARDs given as BSC is not associated with a EULAR response. • Applying a treatment response to BSC to only account for placebo effect would suggest patients would be given a placebo pill to yield this response, which does not happen in clinical practice. The base-case should revert to the treatment sequences and efficacy assumptions that are consistent with the clear precedent set down by the partial review of TA375, as detailed in the previous section.
4	**The rate of progression from moderate to severe disease does not contribute to uncertainty in the cost effectiveness of upadacitinib** AbbVie remains confident in the validity of the base case estimate but accepts the ERG preferred scenario to model the progression of patients from moderate to severe disease. Importantly, sensitivity analysis conducted by AbbVie demonstrated that varying the rate of progression only had a small impact on the ICERs and does not lead to any meaningful uncertainty in cost-effectiveness. This has been confirmed by the independent sensitivity analysis conducted by the Assessment Group for the partial review of TA375, which reached the same conclusion.
5	**The preferred treatment sequence for people whose disease progresses from moderate to severe disease is the most appropriate for decision-making** AbbVie believes the treatment sequences in the preferred scenario for severe disease are the most appropriate for decision-making. The accepted approach in all other RA appraisals has been to position an IL-6 third line in severe disease and so does not contribute to uncertainty in the cost-effectiveness of upadacitinib. During the partial review of TA375, the Assessment Group model was updated to reflect that patients access biologic therapies when their disease progresses to severe RA. This led to the update of the treatment sequences in the base case of the Assessment Group model and positioned tocilizumab third line without any discussion of alternative scenarios. Based on this clear precedent, it would be inappropriate to consider alternative scenarios that included anything other than an IL-6 third line in severe disease. Should the Appraisal Committee feel it necessary to align with precedent, tocilizumab could be inserted instead of sarilumab.

Insert extra rows as needed

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than 1 set of comments from each organisation.

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- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	National Rheumatoid Arthritis Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	As a patient organisation we would of course like to see the availability of the most efficacious therapeutics for people living with rheumatoid arthritis who are in moderate disease activity who, in the opinion of their rheumatologists, would benefit from treatment with such agents. And from the work we have done as an organisation, we are very aware of the enormous, and potentially preventable, suffering that many of our members have as a consequence of denial of access to effective drugs. In light of these remarks, we are disappointed with the recommendations from NICE in the ACD for upadacitinib in moderate disease activity in rheumatoid arthritis. We have two specific points to raise. We note that NICE have indicated that the cost effectiveness of upadacitinib exceeds an arbitrary threshold of £20,000 cost per QALY. And yet our understanding is that in all previous NICE appraisals, the threshold has been (arbitrarily) set at £30,000. Why have NICE made this change?
2	We recognise that health economic modelling is complex and that there is a wide variability in many of the parameters that have to be employed in the model such that the confidence intervals of the estimate of cost effectiveness are wide and may even lack credibility. In the case of this modelling, the use of placebo response data from the RA-Next trial is one such parameter that can legitimately be questioned given that the data reflects mean placebo response rates in an internationally recruited trial when it is well know that there is huge geographical heterogeneity in the context of trials and real world clinical practice. We are not therefore persuaded that the modelling is representative of the UK patient situation although we acknowledge the challenges in arriving at a robust and credible estimate of cost-effectiveness as it applies to the UK population.
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Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or

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the person could be identified.

- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Society for Rheumatology
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The BSR welcomes the opportunity to respond to the ACD on **Upadacitinib for treating moderate rheumatoid arthritis.** We are disappointed that the committee considered that upadacitinib could not be used to treat moderate RA. We feel that the committee may have made inappropriate assumptions in reaching this conclusion. We address our concerns below.
2	NICE Guideline NG 100 recommends that patients with rheumatoid arthritis (RA) should be treated to a target of remission or low disease activity in all patients. In those who fail conventional synthetic disease modifying anti-rheumatoid drugs (csDMARDs) and have persistent moderate disease with a DAS28 >3.2 and ≤ 5.1, there are limited therapeutic options. Currently only filgotinib is currently approved by NICE for these patients. However, patients with persistent moderate disease have increasing disability from observations in several studies: • Conaghan and colleagues (Conaghan PG et al *Rheumatology* 2010;49:1894–1899) found that even over a 6 month period, up to 25% of those with moderate disease had progressive disability. • The Early Rheumatoid Arthritis Study (ERAS)(Jayakumar K et al *Rheumatology* 2012;51:169-75) is a multicentre inception cohort which recruited 1,465 patients with early RA (<2 years disease duration, no prior csDMARD) between 1986 and 1999 from nine hospitals in England, followed yearly for up to 25 years (median follow-up 10 years). The dataset recorded HAQ values of patients at baseline, 6 months, and yearly from year 1 to year 15. We commissioned a detailed analysis of the database. We analysed patients who would be eligible for a biologic drug from TA375 compared with those with persistently moderate disease (patients who had failed methotrexate or at least two non-methotrexate DMARDs or at least one combination DMARD). For those patients who received a TNF inhibitor during the study, only data up to the year prior to the prescription of the TNFi was included in the analysis. There were 868 patients who had a mean DAS28 in the moderate range (119 patients of these patients had a DAS28 that was never >5.1 - 13% of those not in low disease state or remission). In the whole ERAS dataset, 602 patients had high HAQ progression, defined as an annual progression rate ≥0.06. Of these 602 patients, 319 (53%) had moderate RA with a mean DAS28 ≥3.2 and ≤5.1. Therefore approximately a third (36.8%) of all moderate patients had high HAQ progression. • In the Early Rheumatoid Arthritis Network (ERAN) study, Kiely and colleagues (Kiely P et al *Rheumatology* 2011;50:926–31) found that only 52% of 170 patients with moderate disease achieved a Health Assessment Questionnaire score (HAQ) < 1.25 after 2 years despite csDMARDs, compared with 79% of 161 patients who had low disease activity or remission. • In a further analysis of the ERAS and ERAN database, Nikiphorou and colleagues (Nikiphorou E et al *Ann Rheum Dis* 2016;75:2080–2086) found significant progression over time of HAQ independent of whether the DAS score was at the higher or lower part of the moderate range. However, those in the higher range required more orthopaedic surgery. • A recent meta-analysis of 'moderate' RA by Edwards and colleagues (Edwards CJ et al *Rheumatol Adv Pract.* 2019;3:rkz002) concluded that certain factors predicted a worse radiographic, DAS or functional outcome including a DAS towards the upper moderate range and CCP positivity.
3	We note that when modelling updacitinib after failure of a single csDMARD that the ICER exceeds £30,000/QALY compared with modelling after failure of two csDMARDs. We agree with the

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	committee that it is inappropriate to consider advanced therapies unless there has been failure of two csDMARDs. We would support the use of advanced therapies including upadacitinib at that stage.
4	We also agree with the committee that Best Supportive Care is the most appropriate comparator but disagree fundamentally with the ERG that this equates to the placebo response in the SELECT trials. Entry criteria to SELECT-NEXT only required failure of a single csDMARD. It is established that patients have a poor response to other csDMARDs if they have failure of more than one csDMARD. These trials were undertaken with a novel and innovative compound. When entering the study, patients would have had high expectation of a response - reflected in the placebo response. This is in contrast to BSC where a patient is informed that they will remain on a csDMARD that has failed. It cannot be appropriate to then equate the placebo response to BSC. To our knowledge this approach has not been undertaken in previous appraisals in rheumatoid arthritis and we are concerned that this is not a fair assessment.
5	We also have concerns regarding the ERG and committee's understanding of disease progression. The disease activity in an individual with rheumatoid arthritis without treatment tends to persist with a similar degree of disease activity over time. The DAS is a composite score to reflect disease activity. It is not a measure of disability. Patients with moderate DAS have progression in disability and joint damage measured by HAQ and similar parameters (as discussed above) yet remain with a moderate DAS. Only a minority will develop an increase in active synovitis over time reflected by an increase in DAS that may then exceed 5.1 and be labelled as severe. We note that in the ERAN database the committee agreed that 19% of patients increase DAS score from a moderate to a severe range. There is no evidence that a significantly larger number of patients will do so over a longer period of time. Our analysis of the ERAS database does not also suggest that this is a common outcome. We are concerned that the committee may have been misled by the uncertainty of this aspect.
6	We have a major concern regarding the committee's decision to have a threshold of £20,000/QALY. We believe the committee could be accused of acting unfairly in the way they have interpreted NICE's guide to methods of technology appraisal. Upadacitinib is an innovative compound. It therefore falls into the category where it can be approved if an ICER falls between £20,000 to £30,000 range. The methods state: *6.3.3 Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors:* *The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.* *Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained.* *The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure.* *The technology meets the criteria for special consideration as a 'life-extending treatment at the end of life' (see section 6.2.10)* *Aspects that relate to non-health objectives of the NHS (see sections 6.2.20 and 6.2.21).*
7	The Methods do not state that the committee may prefer to adopt an ICER threshold of £20,000/QALY for an innovative technology because of uncertainty. However, in the ACD the committee state: '*Because of this uncertainty, the committee agreed that an acceptable ICER would be around £20,000 per QALY gained.'* We consider this to breach fairness of the process. We also disagree with the grounds of the uncertainty as discussed above. We have reviewed the ICERs from the company's submission and do not agree that the uncertainty would plausibly increase the ICER above £30,000 – the threshold used by NICE for innovative technologies in rheumatoid arthritis for the past fifteen years.

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8	We consider that the development of Janus kinase inhibitors is a major step in the management of rheumatoid arthritis. It is important that clinician's may have a choice of technologies for managing rheumatoid arthritis and this applies to patients with moderate DAS as well as those with more active disease. We hope the committee will review their decidion and approve upadacitinib for these patients.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UCB Pharma
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None to declare
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Section 3.6	Issue statement "the ERG and company considered that the safety profile for upadacitinib is similar to other biological DMARDs". UCB considers the above statement misleading because it does not represent available evidence. Upadacitinib and other JAK inhibitors are not biologic DMARDs (bDMARDs), they are targeted synthetic DMARDs (tsDMARDs). Adverse events from the SELECT-COMPARE trial were numerically higher for upadacitinib than adalimumab, in most cases. The FDA and EMA both issue an additional box warning for upadacitinib and other JAK inhibitors for venous thromboembolism risk, this is not the case with adalimumab or other bDMARDs. Therefore, it is inappropriate to conclude that upadacitinib's safety profile is similar to biological DMARDs.
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Insert extra rows as needed

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Addendum #3 Response to Technical Team Queries – post Company FAC 09/08/2021

1. BACKGROUND

During the course of the assessment the company model has become increasingly complicated by various model revisions for the purposes of running scenarios. These scenarios are no longer relevant and the complexity of the revised model reduces the confidence that can be placed in it. It may also be the reason for the some or all of the disparities between the new ERG modelling and new company modelling.

To try to simply this and achieve agreement between the ERG and the company the ERG reverts to the 29082019 company model which when run for moderate RA estimates an ICER of £21,631 per QALY.

The only proxy that is now required is for upadacitinib + MTX for the treatment of severe RA, the obvious proxy being upadacitinib.

The ERG makes the following changes to the model through reversible drop downs in the Model Settings worksheet, with full cell referencing:

- Applies the following effectiveness estimates:
  - Sets MTX to 9.7% good and 35.5% moderate response
  - Sets intensified csDMARDS to 0% good and 0% moderate
  - Sets all upadacitinib + MTX efficacy to the NEXT.NRI.Mod results
  - Sets all upadacitinib efficacy to NEXT.NRI.SEV results
  - Sets all other b-DMARD efficacy to the b-DMARD-IR NMA results
  - The ERG also explores applying the b-DMARD-IR NMA effectiveness estimates for the use of upadacitinib in severe RA as a scenario analysis.
- Assumes Humira for adalimumab
- Applies the HAQ to DAS28 multiplier of 300%
- Applies the TA375 inpatient costs
- Applies the TA375 HAQ to pain mapping

The ERG appreciates the company sending through its model versions. As some disagreement remains the ERG hopes that the company can work with the now much simplified ERG revised model. With an account of changes made and explicit cell

referencing it will hopefully be possible to relatively easily come to agreement upon modelling results. The ERG is happy to talk through any changes to the model and any disagreements or errors within the model implementation with the company.

From this point forward the ERG will work with two models. One that has never had comparator cPAS percentages inputted to it and an exactly parallel model that has. This means that the ERG can provide the company with a fully working model which will hopefully ease cross checking.

Due to ongoing problems with model stability the ERG has re-run each scenario until two model runs yield the same ICER. The ERG provides electronic copies of the model runs for scrutiny by the company.

2. RESULTS

2.1. Scenario 1

Table 1. Moderate RA treatment sequences

	1st line	2nd line	3rd line
Sequence 1	UPA+MTX	MTX	cDMARDs
Sequence 2	MTX	cDMARDs	..

Abbreviations: cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; UPA, upadacitinib

Table 2. Severe RA treatment sequences

	1st line	2nd line	3rd line	4th line	5th line
Sequence 1	ADA+MTX	RTX+MTX	TCZ+MTX	MTX	cDMARDs
Sequence 2	ADA+MTX	RTX+MTX	TCZ+MTX	MTX	cDMARDs

Abbreviations: ADA, adalimumab; cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab; UPA, upadacitinib

Table 3. Scenario 1 results

	Comparator	UPA+MTX	Net
QALYs	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]
ICER			£3,410

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; MTX, methotrexate; UPA, upadacitinib

2.2. Scenario 2

Table 4. Moderate RA treatment sequences

	1st line	2nd line	3rd line
Sequence 1	UPA+MTX	cDMARDs	..
Sequence 2	MTX	cDMARDs	..

Abbreviations: cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; UPA, upadacitinib

Table 5. Severe RA treatment sequences

	1st line	2nd line	3rd line	4th line	5th line
Sequence 1	ADA+MTX	RTX+MTX	TCZ+MTX	MTX	cDMARDs
Sequence 2	ADA+MTX	RTX+MTX	TCZ+MTX	MTX	cDMARDs

Abbreviations: ADA, adalimumab; cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab; UPA, upadacitinib

Table 6. Scenario 2 results

	Comparator	UPA+MTX	Net
QALYs	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]
ICER			£21,683

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; MTX, methotrexate; UPA, upadacitinib

2.3. Scenario 3

Table 7. Moderate RA treatment sequences

	1st line	2nd line	3rd line
Sequence 1	UPA+MTX	MTX	cDMARDs
Sequence 2	MTX	cDMARDs	..

Abbreviations: cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; UPA, upadacitinib

Table 8. Severe RA treatment sequences

	1st line	2nd line	3rd line	4th line	5th line
Sequence 1	ADA+MTX	RTX+MTX	TCZ+MTX	MTX	cDMARDs
Sequence 2	ADA+MTX	RTX+MTX	UPA+MTX	MTX	cDMARDs

Abbreviations: ADA, adalimumab; cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab; UPA, upadacitinib

Table 9. Scenario 3 results

	Comparator	UPA+MTX	Net
QALYs	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]
ICER			£24,866

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; MTX, methotrexate; UPA, upadacitinib

2.4. Scenario 4

Table 10. Moderate RA treatment sequences

	1st line	2nd line	3rd line
Sequence 1	UPA+MTX	cDMARDs	..
Sequence 2	MTX	cDMARDs	..

Abbreviations: cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; UPA, upadacitinib

Table 11. Severe RA treatment sequences

	1st line	2nd line	3rd line	4th line	5th line
Sequence 1	ADA+MTX	RTX+MTX	TCZ+MTX	MTX	cDMARDs
Sequence 2	ADA+MTX	RTX+MTX	UPA+MTX	MTX	cDMARDs

Abbreviations: ADA, adalimumab; cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab; UPA, upadacitinib

Table 12. Scenario 4 results

	Comparator	UPA+MTX	Net
QALYs	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]
ICER			£51,212

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; MTX, methotrexate; UPA, upadacitinib

2.5. Scenario 5

Scenario 5 is as per Scenario 3 but applies the b-DMARD-IR NMA effect estimates for UPA+MTX in severe RA.

Table 13. Moderate RA treatment sequences

	1st line	2nd line	3rd line
Sequence 1	UPA+MTX	MTX	cDMARDs
Sequence 2	MTX	cDMARDs	..

Abbreviations: cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; UPA, upadacitinib

Table 14. Severe RA treatment sequences

	1st line	2nd line	3rd line	4th line	5th line
Sequence 1	ADA+MTX	RTX+MTX	TCZ+MTX	MTX	cDMARDs
Sequence 2	ADA+MTX	RTX+MTX	UPA+MTX	MTX	cDMARDs

Abbreviations: ADA, adalimumab; cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab; UPA, upadacitinib

Table 15. Scenario 5 results

	Comparator	UPA+MTX	Net
QALYs	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]
ICER			£23,570

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; MTX, methotrexate; UPA, upadacitinib

2.6. Scenario 6

Given the recent recommendations for the use of generic biologics for moderate disease the ERG augments Scenario 4 with the following.

Table 16. Moderate RA treatment sequences

	1st line	2nd line	3rd line
Sequence 1	UPA+MTX	cDMARDs	..
Sequence 2	MTX	cDMARDs	..

Abbreviations: cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; UPA, upadacitinib

Table 17. Severe RA treatment sequences

	1st line	2nd line	3rd line	4th line	5th line
Sequence 1	ADA+MTX	RTX+MTX	TCZ+MTX	MTX	cDMARDs
Sequence 2	ADA+MTX	RTX+MTX	UPA+MTX	MTX	cDMARDs

Abbreviations: ADA, adalimumab; cDMARDs, conventional disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab; UPA, upadacitinib

Table 18. Scenario 6 results

	Comparator	UPA+MTX	Net
QALYs	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]
ICER			£45,575

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; MTX, methotrexate; UPA, upadacitinib

3. SUMMARY

A summary of the ERG modelling results are presented below (Table 19), together with the relevant company estimates.

Table 19. Summary of results

	ICER	
	ERG	**Company**
Scenario 1	£3,410	£5,908
Scenario 2	£21,683	£20,202
Scenario 3	£24,866	n.a.
Scenario 4	£51,212	n.a.
Scenario 5	£23,570	£23,160
Scenario 6	£45,575	£43,488

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; n.a., not applicable

The company objects to the consideration of whether it is cost effective to change the upadacitinib recommendation from the current position for use in severe RA to being used to treat moderate RA. The reasoning behind this objection is not clear. As with all the modelling, the ERG acknowledges that it requires assumptions and is subject to uncertainty.

Thank you for the opportunity to consider the differences between the company ICERs and ERG ICERs and identify the source of discrepancy. We have reviewed both models and identified two implementation errors in the ERG model, which, once corrected for lead to similar ICERs between the company model and ERG model across scenarios 1 and 2.

1. Efficacy inputs used for ADA+MTX in the intervention (upadacitinib) arm should be based on the b-DMARD-IR NMA, with ETN+MTX used a proxy for the efficacy of ADA+MTX and efficacy inputs used for ADA+MTX in the comparator arm should be based on the c-DMARD-IR NMA.
2. Administration costs associated with rituximab have been incorrectly implemented and should be doubled to account for administration costs over two weeks rather than one week

AbbVie has assessed the models shared by the ERG and has identified two issues that merit updates in the ERG model. After the updates, AbbVie agrees that the ERG model is suitable for decision making. AbbVie has re-run the models with the two updates implemented to the ERG model and summarised the ICERs for scenarios 1-2.

AbbVie has identified the following two implementation errors with the ERG model:

1. **ADA+MTX efficacy in UPA arm vs. comparator arm**

   ADA+MTX appear in both sequence 1 and 2, however, the efficacy for ADA+MTX in UPA arm should be based on b-DMRAD-IR NMA, the efficacy for ADA+MTX in comparator arm should be based on c-DMARD-IR NMA. As a result, a proxy arm is needed. ETN+MTX is used as a proxy for efficacy of ADA+MTX in severe b-DMARD-IR RA in UPA arm.

	Efficacy inputs in the ERG models	**Proposed efficacy inputs**
ADA+MTX in UPA arm (for all sequence 1 under severe RA treatment sequences)	Good: 0.30, Moderate: 0.27	Good: 0.30, Moderate: 0.27 (based on b-DMARD-IR NMA) (Used r; and the drug costs [AC42:AE42 in "Drug costs" tab] have been updated to be the same as ADA+MTX)
ADA+MTX in comparator arm (for all sequence 2 under severe RA treatment sequences)	Good: 0.30, Moderate: 0.27	Good: 0.38, Moderate: 0.30 (this should be based on c-DMARD-IR NMA) (efficacy inputs updated in K97:N97 of "Efficacy" tab)

2. **Administration cost of RTX should be doubled**

The approved dosing for rituximab in the UK is 2,000 mg every 9 months.[1] The dose is split over 2 weeks (i.e., 1,000 mg week 1 and 1,000 mg week 2). Therefore, the administration costs should be double that of the current value. AbbVie has updated AC48 and AE48 of "Drug costs" tab to reflect this.

After fixing these two issues with the ERG model, ICERs for scenarios 1 and 2 are the same as the AbbVie model. In the interest of time, AbbVie has run scenarios 1 and 2 only with the two updates to the ERG model. The resulting ICERs are summarised in the table below, alongside the ICERs in the original ERG model and AbbVie model.

ERG scenarios	ICER in original ERG model	ICER in AbbVie updated ERG model	ICER in AbbVie model
Scenario 1	£7,484	£3,410	£3,410
Scenario 2	£24,455	£21,683	£21,683

We therefore maintain the robustness of the AbbVie model for decision making and once the updates relating to the errors mentioned above have been implemented, the ERG model is also suitable for decision making. Additionally, we maintain our position that scenario 1 is the only relevant scenario to conclude decision making for this appraisal, aligned with the assumptions and settings used to inform decision-making in the partial review of TA375 (TA715].

[1] https://www.nice.org.uk/guidance/ta195/chapter/3-The-technologies#rituximab