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:

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. British Society for Rheumatology
   b. UCB Pharma Ltd

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

5. **ICERs requested by NICE prior to second appraisal committee meeting** prepared by **Peninsula Technology Assessment Group**

6. **ERG additional analyses after AC2** prepared by **Peninsula Technology Assessment Group**

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

Upadacitinib for treating severe rheumatoid arthritis

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	We are grateful for the opportunity of responding to the ACD on upadacitinib in rheumatoid arthritis and are pleased that NICE have recommended treatment for patients with severe disease. However, we are disappointed that NICE have failed to approve effective treatment for patients with moderate disease ie those with a disease activity score between 3.2 and 5.1. This group of patients have significant symptoms and progressive disability and yet if they fail disease modifying anti-rheumatic drugs they do not have any other available treatment other than best supportive care. Clinical trial data with upadacitinib has shown this treatment to be effective in both severe and moderate rheumatoid arthritis. Trials have demonstrated efficacy with upadacitinib that is at least as effective as adalimumab: ACD p10 *"The trials show upadacitinib is more clinically effective than adalimumab, conventional DMARDs (including methotrexate) or placebo for moderate to severe disease that has responded inadequately to conventional DMARDs."* Following TA 375 Stevenson and colleagues from ScHARR stated "Exploratory analyses indicate that if the price of bDMARD (excluding RTX) were reduced by 50%, the mean ICER would decline to £24,500 for patients with severe RA and £31,500 for patients with moderate to severe RA." (*Stevenson M et al J Rheum 2017; 44:973-80*). The price of [redacted] is less than [redacted] of the cost adalimumab in the TA375 analysis and at least as effective. Its place in the treatment pathway is similar. It is inconceivable that it is not cost-effective in moderate rheumatoid arthritis if the same methodology used in TA 375 is undertaken. We consider the approach taken by the ERG to lead to this negative recommendation for moderate rheumatoid arthritis is flawed and is different to all previous appraisals at least in rheumatology. As such it is our view that if the ACD is not revised that NICE would be failing to act fairly in the evaluation of this technology. 3.11 p15 "*The ERG advised that some proportion of the upadacitinib response seen in the clinical trials would be caused by the same placebo effect seen in the control arms. The ERG therefore preferred to apply the placebo response from the network meta-analysis to best*	Thank you for your comments. Please note that this technology appraisal has been split into 2 separate topics. The final appraisal document (FAD) for people with severe rheumatoid arthritis has now been published and upadacitinib is recommended for specific groups. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.

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
			supportive care when it was compared with upadacitinib. The committee recalled that the clinical expert would not expect best supportive care to give a treatment response at this position. However, it agreed that the placebo effect will be present in the upadacitinib response rates. Therefore, comparing this with a 0% response rate would overestimate the effectiveness of upadacitinib relative to best supportive care. The committee concluded that it was not appropriate to apply a 0% response rate for best supportive care while also applying the full, observed response rate for upadacitinib." We consider this is an unsupported supposition by the ERG not based on published evidence. It is beyond logic to consider that a patient not receiving any new treatment and being treated with best supportive care would have a placebo response. This implies that, for example, a patient may fail to achieve remission or low disease state with methotrexate would have treatment withdrawn and then recommenced and have a better response because of a placebo response. In clinical practice disease modifying anti-rheumatic drugs are usually continued in moderate rheumatoid arthritis, not stopped and restarted. NICE guidelines are to use combination therapies in a step up approach and to step down only if the target of remission or low disease state (NG100 1.4.3). In those with moderate disease there is no indication to withdraw then recommence treatment. We recommend that the ERG revise their recommendation and undertake an analysis that reflects the reality of treatment.	
2		British Society for Rheumatology	Upadacitinib is a novel JAK 1 specific inhibitor, effective in treating high disease activity rheumatoid arthritis. Clinical data suggests that its efficacy in terms of ACR20 response, in combination with methotrexate, is superior to that of adalimumab in combination with methotrexate	Thank you for your comments. Please note that this technology appraisal has been split into 2 separate topics. The FAD for people with severe rheumatoid arthritis has now been published and upadacitinib is recommended for specific groups. A second consultation is in progress following the second appraisal committee

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
				meeting. This will cover moderate rheumatoid arthritis. .
3		British Society for Rheumatology	Upadacitinib is a useful and welcome addition to the range of drugs available for the treatment of severe rheumatoid arthritis.	Please note that this technology appraisal has been split into 2 separate topics. The FAD for people with severe rheumatoid arthritis has now been published and upadacitinib is recommended for specific groups. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.
4		British Society for Rheumatology	I believe that all the relevant clinical data has been taken into account	Thank you, your comment has been noted.
5		British Society for Rheumatology	The provisional recommendations for severe disease are similar as those issued for the other JAK inhibitors – baricitinib and tofacitinib in rheumatoid arthritis. These recommendations are sound and a suitable basis for guidance to the NHS	Thank you, your comment has been noted.
6		British Society for Rheumatology	It is very disappointing that upadacitinib has not been recommended for use in moderate rheumatoid arthritis patients. Moderate disease activity is associated with reduced quality of life, increasing disability, deterioration in function (as assessed by HAQ score) and structural damage progression. Presently such patients have not been deemed eligible by NICE for advanced therapies and thus a large percentage will continue to deteriorate, without a chance of achieving our goal of disease remission, and often requiring medications, such as corticosteroids, which are known to have a high risk of side effects	Thank you for your comments. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.

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7		British Society for Rheumatology	I have no other comments	Comment noted.
8		UCB Pharma Ltd	UCB believes that the does not provide enough evidence for decision-making in moderate population e.g. number of treatment failures. There is no consistent outcome in terms of treatment effect as the number of treatment failures increases. This contradicts with company's common effects NMA assumption in the treatment pathway. Overall, this may impact the cost-effectiveness results.	Thank you for your comments. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.
9		UCB Pharma Ltd	UCB believes that the appropriate comparator for the moderate disease after 2 conventional DMARDs is best supportive care, which is unlikely to give an EULAR response.	Comment noted. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.
10		UCB Pharma Ltd	UCB believes that comparing treatment sequences of different lengths may result in a misleading result.	Comment noted. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.
11		UCB Pharma Ltd	UCB believes that "net treatment effect" is misleading as this analysis does not include other factors who may have an impact on the model e.g. natural recovery. UCB agrees with ERG that the response rate for upadacitinib may underestimate the treatment cost in the model, compared with what would be expected in clinical practice	Thank you for your comments. A second consultation is in progress following the second appraisal committee meeting. This will cover

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				moderate rheumatoid arthritis.
12		UCB Pharma Ltd	UCB recommends that HAQ trajectories should be considered as these have been incorporated for both UPA and BSC responders.	Thank you for your comments. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.
13		UCB Pharma Ltd	UCB believes that the company underpredict the transition rate from moderate to severe in their base scenario concerning based on the literature (Kiely et al). This underprediction has a clear impact on the cost-effectiveness results in favour of UPA.	Thank you for your comments. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.
14		UCB Pharma Ltd	UCB believes that larger datasets provide a more confident and robust source of information thus TA375 is preferred.	Thank you for your comments. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.
15		UCB Pharma Ltd	UCB believes that there is no consistency with TA375 in how the moderate sub-group has been modelled. That it would be useful for the ACD to provide this context as this may add further uncertainty to the submitted CE analysis for the moderate population which may have an impact on the final ICER acceptable range.	Thank you for your comments. A second consultation is in progress following the

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				second appraisal committee meeting. This will cover moderate rheumatoid arthritis.
16		UCB Pharma Ltd	UCB believes that for consistency, the ACD should not include language along the lines of what was included in the CZP PsO guidance. As immunology is a crowded space and if NICE included that statement for CZP in PsO then UCB believes that this should be applicable in Ra space as well. Upadacitinib rec: *"It recommends treatment should start with the least expensive drug (taking into account administration costs, dose needed and product price per dose) and should only be continued according to European League Against Rheumatism (EULAR) response at 6 months."* CZP (PsO) rec: *"If patients and their clinicians consider certolizumab pegol to be one of a range of suitable treatments, the least expensive should be chosen (taking into account administration costs, dosage, price per dose andcommercial arrangements)"*	Thank you for your comments. No changes have been made. This is consistent with other technology appraisal guidance for rheumatoid arthritis.
17		AbbVie Ltd.	Thank you for the opportunity to comment on the appraisal consultation document (ACD) for upadacitinib for previously treated moderate to severe active rheumatoid arthritis (RA). We welcome the Committee's recommendation for the use of upadacitinib as an option for treating severe RA. We remain committed to resolving any remaining issues in moderate RA to enable patient access to upadacitinib in this area of extremely high unmet need. AbbVie believes that the changes to the modelling approach outlined in the ACD diverge from clinical practice, and from the precedents set in previous RA appraisals, including the previous multiple technology appraisal (TA375). Importantly, aligning with clinical practice and past precedent would lead to an ICER of £25,111 in moderate RA rather than an ICER exceeding £30,000, based on AbbVie's understanding of preferred assumptions within the ACD. Compared with the TA375 model, the AbbVie model provides broadly comparable ICERs. Using the AbbVie model to reproduce the analysis of adalimumab in moderate RA in TA375, the AbbVie model estimated an ICER of £55,866 compared to £51,472 reported in TA375. AbbVie acknowledge the comments outlined in the ACD around treatment waning and the number of patients transitioning from moderate to severe RA and suggest scenarios which address these issues.	Thank you for your comments. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.

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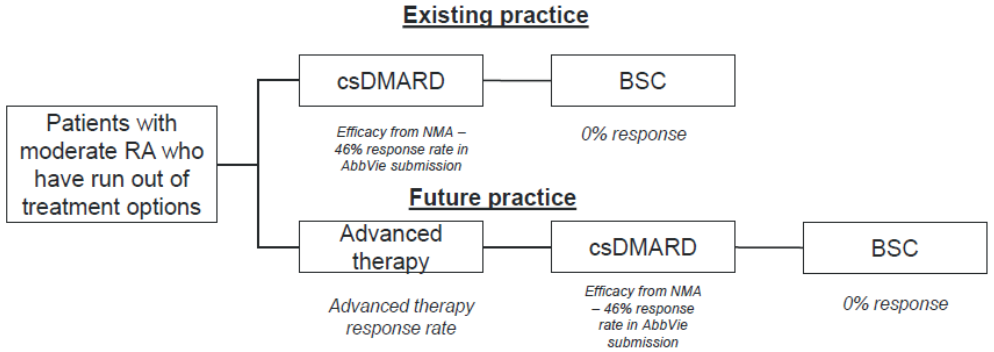
			Healthcare professionals and patients have been waiting a long time for an advanced therapy to be available and funded in moderate RA. AbbVie is committed to working with NICE to enable immediate access to this oral therapy, which is the first JAK inhibitor to demonstrate statistically significantly better outcomes for patients compared to adalimumab plus methotrexate . AbbVie has previously proposed a confidential discount that makes upadacitinib cost-effective in this population, based on the modelling approaches adopted in TA375 and precedents from subsequent appraisals. In order to ensure the fairness, objectivity and reasonableness of the upadacitinib appraisal, it is essential that the Committee continues to conduct its analysis in a manner consistent with the methodology used in previous appraisals for RA.	
18		AbbVie Ltd.	**The assumption that the upadacitinib response rate includes a placebo effect component whilst that of csDMARDs does not, substantially increases the ICER of upadacitinib in moderate RA and is inconsistent with clinical practice and the precedent set in previous appraisals** To aid clarity, Figure 1 schematically represents the original approach submitted by AbbVie, which is aligned to TA375 and subsequent appraisals. Figure 2 represents the approach advocated by the committee as outlined in the ACD. **Figure 1 - Sequence A: Approach used in TA375 and the subsequent three NICE appraisals of RA drugs (baricitinib, tofacitinib and sarilumab) and in the AbbVie original submission**  **Figure 2 - Sequence B: Approach advocated by the committee in the ACD for upadacitinib in RA**	Thank you for your comments. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.

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			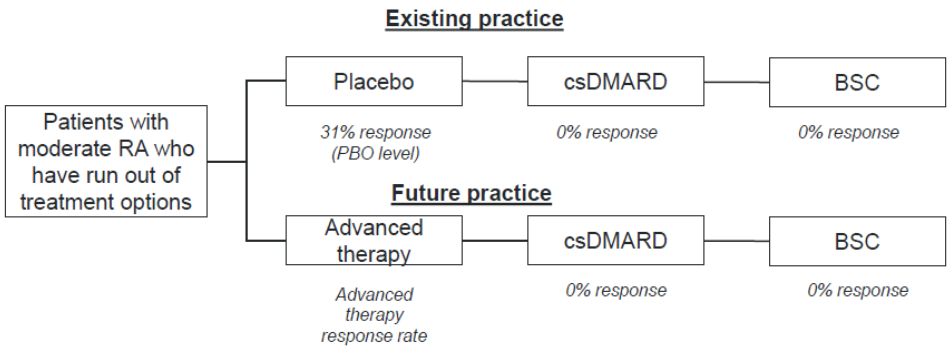 The ACD states that patients who have failed two or more csDMARDs would receive a csDMARD which at this stage is associated with a 0% response rate: *"The committee concluded that after 2 conventional DMARDs, previously used conventional DMARDs with optional corticosteroids would constitute best supportive care. This was the most appropriate comparator to upadacitinib because it reflected clinical practice. The committee also concluded that best supportive care was unlikely to give an EULAR response" (page 14).* In addition, it is assumed that the efficacy of upadacitinib is associated with a placebo related component and to account for this the ERG *"preferred to apply the placebo response from the NMA to BSC when it was compared with upadacitinib"* (page 15). The ERG's preferred source for this placebo response rate is the company's NMA which estimates a 31% response rate for placebo. AbbVie believes that the assumption of a placebo response component included in the efficacy of upadacitinib means that, to be consistent, a placebo response should similarly be assumed for csDMARD. This placebo response rate should be the same as that assumed for the upadacitinib arm, namely 31%. This 31% placebo response should be the "floor efficacy" that can be associated with csDMARD when it is used in patients who have tried and failed all other options; even if the drug has zero efficacy associated with its bioactive ingredients it would display a placebo effect. AbbVie continue to support the approach established in TA375 (and the three subsequent NICE RA appraisals) shown in Figure 1 which sources the efficacy of csDMARD in the	

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			comparator arm and in the intervention arm after the failure of the advanced therapy from the NMA. However, as a sensitivity analysis, (if a lower efficacy than that that estimated in the NMA is thought likely to be displayed in clinical practice) the "floor" for this efficacy should be "placebo effect" which in this appraisal has been estimated to be 31%, addressed in Table 6. AbbVie note that in the NICE preferred approach (Figure 2), a placebo has been included in the comparator arm. This is an artificial mechanism to net off placebo from the comparator arm and as such its inclusion does not reflect clinical practice.	
19		AbbVie Ltd.	**The ACD suggests that the relative effectiveness of active treatment is overestimated in treatment sequences of unequal lengths. Constraining sequences means all the benefits that will manifest in UK clinical practice are not captured adequately.** The ACD states that treatment sequences of different length may bias the model in favour of the longer sequence. The rationale for equalising treatment sequences from the ACD is: *"The ERG advised that having unequal sequence lengths means at some point, an active treatment in the longer sequence is at the same position as best supportive care in the shorter sequence. The relative effectiveness of the active treatment at this point may be overestimated if best supportive care has no response rate" (page 14).* The ERG claim that by modelling the treatment sequences observed in clinical practice, the effectiveness of the intervention is *over*estimated is unsubstantiated by any evidence. In sequence A above (Figure 1), AbbVie believe the overestimation asserted by the Committee applies to a patient receiving a csDMARD after upadacitinib failure. To net off all this benefit, would be to negate the benefit of csDMARD in this position. The evidence for this approach has not been specified and means that the modelling would not reflect the benefits that will manifest in UK clinical practice. The ACD does not include a rationale of what is meant by an overestimation of an active treatment. This issue is explained in more detail in issue 3. The second reason expressed in the ACD by the Committee for equalising treatment sequences, is as follows: *"The clinical expert advised that in practice, any DMARD treatment would be expected to have a lower response rate the later it is used in the treatment pathway, compared with if it was used earlier. This was not captured in the network meta-analysis, which assumes a constant effect of each treatment regardless of its pathway position. So, the ERG explained it was likely that the model overestimated the response rate of treatments at later lines in the pathway. This*	Thank you for your comments. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.

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			means the cost-effectiveness model is further biased in favour of the arm with the longest treatment sequence (upadacitinib). The committee concluded that unequal treatment lengths may bias cost-effectiveness results" (page 14-15). This issue of waning of efficacy in later lines of therapy though can be addressed by applying a 5% waning of efficacy for third line use relative to second line and fourth line use relative to third line (second line efficacy is already lower than first line in the model results presented by the company in our technical engagement response because it sources values from the advanced therapy experienced NMA). The impact of this assumption upon ICERs is addressed in Table 4 to Table 6. This 5% waning rate is in line with the following estimation made by the clinical advisor quoted in the technical engagement report below. *"Regarding the magnitude of benefit a treatment provides at different lines in the treatment pathway, the clinical expert advised that bDMARDs are expected to give a lower response rate with each passing line of therapy (approximately 5% less each time)" (page 36 of the final technical report).*	
20		AbbVie Ltd.	**The ACD provides a statement that an active drug when compared to BSC will result in an overestimation of the efficacy of the active drug as a rationale for equalising treatment sequences. It does not explain what it means by "overestimation"** The ACD provides the following rationale for equalising treatment sequences between the intervention and comparator arms: *"The ERG advised that having unequal sequence lengths means at some point, an active treatment in the longer sequence is at the same position as best supportive care in the shorter sequence. The relative effectiveness of the active treatment at this point may be overestimated if best supportive care has no response rate" (page 14).* The modelling approach followed by AbbVie (aligned to TA375 and the subsequent three NICE RA drug appraisals) involves unequal treatment sequences between the intervention and comparator arms reflecting clinical practice. The ACD provides no explanation of what is meant by *"overestimated"* in this situation despite it being a rationale for rejecting past precedence. AbbVie note that Addendum 4 to the ERG Report provides a potential explanation for the Committee's approach where the ERG states: *"Suppose that all biologic trials the active intervention arm had a response rate of 35% while the sugar pill/control/placebo had a response rate of 30%. [New Paragraph] The company*	Thank you for your comments. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.

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			position is that the biologic warrants an NHS price wholly attributes the 35% response rate to the biologic. The ERG position warrants an NHS price that only attributes the net additional 5% response rate to the biologic." (page 7 in section 2.4 titled How to net out control / placebo effectiveness) The implication of this statement is that the ERG believe that placebo effect should be netted off a new intervention because the NHS should not reimburse it and to not do so involves an "overestimation" of the efficacy of that new intervention. However, in the case of the unequal treatment sequences in the AbbVie preferred model (aligned to TA375 and reproduced in Figure 1, Issue 1) it is a csDMARD which is on the same line of therapy as BSC, and as such the "overestimation" relates to the efficacy of a csDMARD in this position. Since this is not the intervention under appraisal but is already reimbursed by the NHS, the ERG's rationale in Addendum 4 is no longer relevant.	
21		AbbVie Ltd.	**The ERG have failed to correct two of the four implementation errors they made to the health economic model.** Correcting for all four implementation errors by the ERG shows that the ICERs using the AbbVie model are broadly comparable (using sequence 1 as the reference case) to ICERs using TA375. This repeats the analysis carried out by the ERG in Addendum 4 of the ERG report in which only two of the four implementation errors are corrected and which concluded that *"The company model validation work of its addendum 3 appears to suggest that the company model is more favourable to the biologic sequences when comparing them with non-biologic containing sequences than the TA375 model"*. The two additional errors are as follows: • The incorrect implementation of efficacy values for all drugs (the ERG used the percentage of moderate responders in the TA375 model in cells in which total responders i.e. Moderate plus good responders were required) • The use of INT_CON_DMARD, instead of the more appropriate option of TICORA, to simulate intensive csDMARD. INT_CON_DMARD is associated with a 0% discontinuation rate after the first six months unlike TICORA which is associated with discontinuation rate curves aligned to those used in TA 375 and the AbbVie model (and hence greater than zero for the life-time of the model) As shown in Table 1 and Table 2 below correcting for all four implementation errors and repeating the analysis upon which the ERG's conclusion was made shows a close match for four of the seven ICERs between the models (2%-5% difference) with one ICER more	Thank you for your comments. A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis. .

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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>
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favourable using the AbbVie model (by 17%) and two less favourable (by 17% and 40%). AbbVie provide more detail on this point in a document submitted as part of this ACD response.

Table 1: Comparison of AbbVie model output to TA375 model output correcting for all four implementation errors
<table>
<tr><th colspan="6">Using AbbVie model</th><th rowspan="2">ICERs (AbbVie model relative to TA375 model output)</th></tr>
<tr><th></th><th>Costs</th><th>QALYs</th><th>Incremental costs (relative to SEQ 1)</th><th>Incremental QALYs (relative to SEQ 1)</th><th>ICERs</th></tr>
<tr><td>Sequence 1</td><td>71,311</td><td>7.26</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Sequence 2</td><td>88,786</td><td>7.91</td><td>17,475</td><td>0.65</td><td>26,885</td><td>98%</td></tr>
<tr><td>Sequence 3</td><td>93,513</td><td>7.93</td><td>22,202</td><td>0.67</td><td>33,137</td><td>83%</td></tr>
<tr><td>Sequence 4</td><td>104,501</td><td>8.03</td><td>33,190</td><td>0.77</td><td>43,104</td><td>96%</td></tr>
<tr><td>Sequence 5</td><td>106,173</td><td>7.65</td><td>34,862</td><td>0.39</td><td>89,390</td><td>140%</td></tr>
<tr><td>Sequence 6</td><td>112,602</td><td>7.71</td><td>41,291</td><td>0.45</td><td>91,758</td><td>117%</td></tr>
<tr><td>Sequence 7</td><td>125,581</td><td>8.28</td><td>54,270</td><td>1.02</td><td>53,206</td><td>97%</td></tr>
<tr><td>Sequence 8</td><td>127,589</td><td>8.28</td><td>56,278</td><td>1.02</td><td>55,175</td><td>95%</td></tr>
</table>
Table 2: TA375 model output
<table>
<tr><th colspan="6">Using TA375 model</th></tr>
<tr><th></th><th>Costs</th><th>QALYs</th><th>Incremental costs (relative to SEQ 1)</th><th>Incremental QALYs (relative to SEQ 1)</th><th>ICERs</th></tr>
<tr><td>Sequence 1</td><td>73,841</td><td>7.25</td><td></td><td></td><td></td></tr>
<tr><td>Sequence 2</td><td>90,596</td><td>7.86</td><td>16,755</td><td>0.61</td><td>27,467</td></tr>
<tr><td>Sequence 3</td><td>98,166</td><td>7.86</td><td>24,325</td><td>0.61</td><td>39,877</td></tr>
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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
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Sequence 4</td><td>111,463</td><td>8.09</td><td>37,622</td><td>0.84</td><td>44,788</td></tr>
<tr><td>Sequence 5</td><td>112,773</td><td>7.86</td><td>38,932</td><td>0.61</td><td>63,823</td></tr>
<tr><td>Sequence 6</td><td>124,989</td><td>7.9</td><td>51,148</td><td>0.65</td><td>78,689</td></tr>
<tr><td>Sequence 7</td><td>135,277</td><td>8.37</td><td>61,436</td><td>1.12</td><td>54,854</td></tr>
<tr><td>Sequence 8</td><td>138,894</td><td>8.37</td><td>65,053</td><td>1.12</td><td>58,083</td></tr>
</table>

Of relevance to this issue is the validation exercise submitted to NICE on the 8th November in which we reproduce the analysis of adalimumab in moderate RA carried out in TA375 using the AbbVie model. This showed the AbbVie model providing a less preferential ICER (£55,866) compared to that reported in TA375 (£51,472).</td><td></td></tr>
<tr><td>22</td><td></td><td>AbbVie Ltd.</td><td>
<u>The ACD states that AbbVie's health economic model is not robust because the rate of transition for moderate RA patients to severe RA advanced therapies in the model is lower than that observed in clinical practice. AbbVie present an additional analysis which addresses this issue.</u>

In the ACD it is stated that that the cost effectiveness estimates for moderate RA are thought not to be robust because the rate of transition to severe RA advanced therapies in the health economic model is lower than that observed in clinical practice. While we remain confident in the validity of this estimate, the assumed rate has a negligible effect on the ICER. In the analysis presented in AbbVie's original ACD response which used discounted prices for adalimumab and assumed discounts for sarilumab and rituximab, using the extreme assumption of 87% of patients transitioning to severe RA only increases ICERs by 10% (list prices for all comparators are used in this version of our ACD response following a request from NICE on 18th August 2020)

The percentage of patients transitioning to severe RA at two years in the comparator arm is about 19% if the transition rate is tripled compared to the baseline rate (by tripling the DAS 28 to HAQ ratio relative to baseline). The rate is similar to the ERAN database study consisting of newly diagnosed and csDMARD-treated patients. It should be noted that transition to severe RA in the model is linked to change in HAQ which in turn is assumed (based upon TA375 assumptions) to be the same in csDMARD treated and untreated patients. It is also worth noting that the HAQ curves based on Norton et al., are broadly linear in the first six years after which increases start to flatten out.

Table 3: Transition from moderate RA to severe RA advanced therapies (comparator arms for both NICE and AbbVie preferred approaches)
<table>
<tr><th></th><th>Year 2</th><th>Maximum (by year</th></tr>
</table>
</td><td>Thank you for your comments.

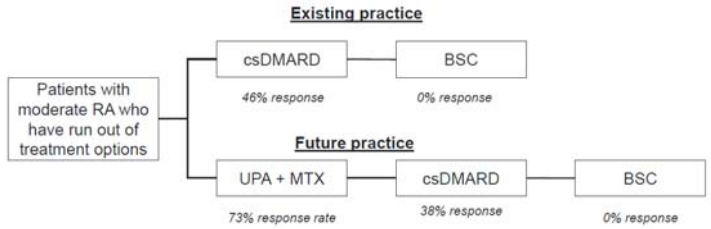
A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.</td></tr>
</table>

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

		12)
Base case transition to advanced therapies	5%*	33%*
Double base case transition to advanced therapies	11%*	71%*
Triple base case transition to advanced therapies	19%*	87%*

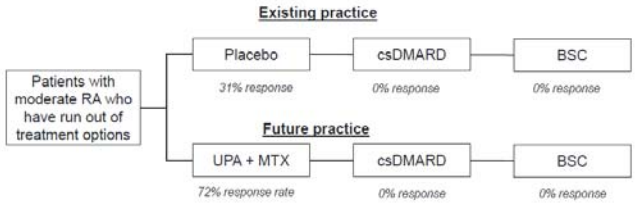
** of surviving cohort*

Table 4: Methotrexate eligible patients AbbVie preferred approach (UPA + MTX)

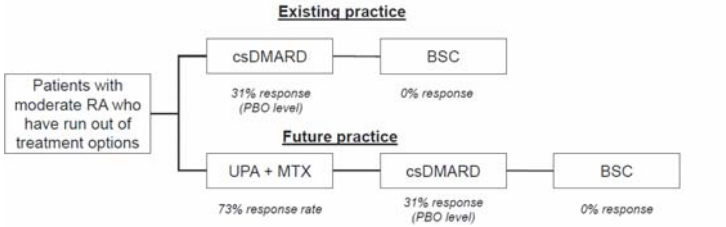
	**ICERs**
Scenario 1: Using list prices for drugs other than upadacitinib	£25,110
Scenario 2: Assume no transition to severe RA advanced therapies	£29,557
Scenario 1 PLUS 5% waning assumed* (base case transition to advanced therapies)	£25,462
Scenario 1 plus 5% waning assumed* (double base case transition to advanced therapies)	£18,428
Scenario 1 plus 5% waning assumed* (triple base case transition to advanced therapies)	£13,492

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line*

Table 5: Methotrexate eligible patients using NICE preferred approach (UPA + MTX)

	**ICERs**
Scenario 1: Using list prices for all drugs except upadacitinib	£29,501
Scenario 2: Assume no transition to severe RA advanced therapies	£33,320

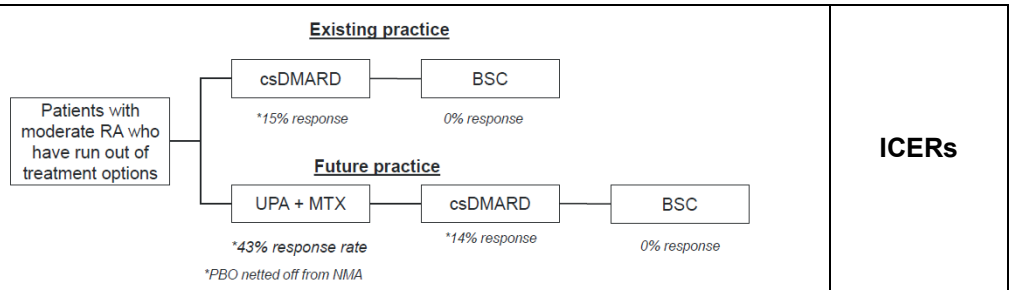
<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Scenario 1 PLUS 5% waning assumed* (base case transition to advanced therapies)</td><td>£30,600</td></tr>
<tr><td>Scenario 1 plus 5% waning assumed* (double base case transition to advanced therapies)</td><td>£25,661</td></tr>
<tr><td>Scenario 1 plus 5% waning assumed* (triple base case transition to advanced therapies)</td><td>£21,773</td></tr>
</table>
* in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line

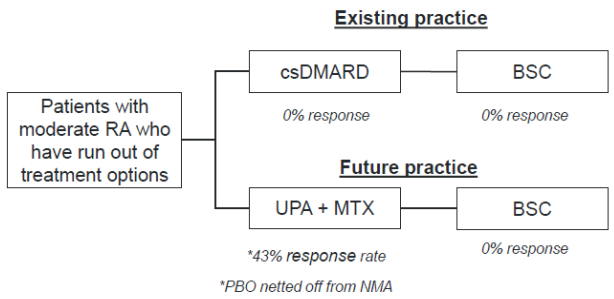
Table 6: Methotrexate eligible patients AbbVie approach – sensitivity analysis placebo efficacy “floor” for assumed lower bound efficacy of csDMARD (UPA + MTX)
<table>
<tr><td> 
</td><td>ICERs</td></tr>
<tr><td>List prices for all drugs except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)</td><td>£20,501</td></tr>
<tr><td>List prices for all drugs except upadacitinib PLUS 5% waning assumed* (Double base case transition to advanced therapies)</td><td>£12,484</td></tr>
<tr><td>List prices for all drugs except upadacitinib PLUS 5% waning assumed* (Triple base case transition to advanced therapies)</td><td>£6,354</td></tr>
</table>
* in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line
</td><td></td></tr>
<tr><td>23</td><td></td><td>AbbVie Ltd.</td><td><u>The ACD misrepresents the intention of the company’s ‘net treatment effect’ approach</u>

On page 16 of the ACD the following is stated:

“[Heading of section] The company’s ‘net treatment effect’ analysis may be appropriate to model effectiveness of upadacitinib relative to best supportive care, but not the relative costs. [New Paragraph] 3.12: In its response to technical engagement, the company provided a scenario analysis which estimated the ‘net treatment effect’ of upadacitinib relative to the trial control arms. This decreased the upadacitinib response rate to reflect that some of the overall response could be because of a trial or placebo effect. In this analysis, the company used the</td><td>Thank you for your comment.

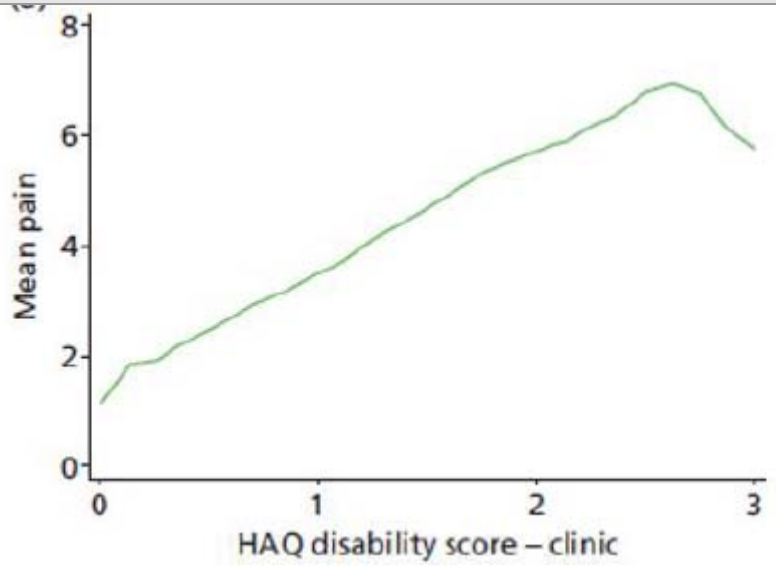
A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.</td></tr>
</table>

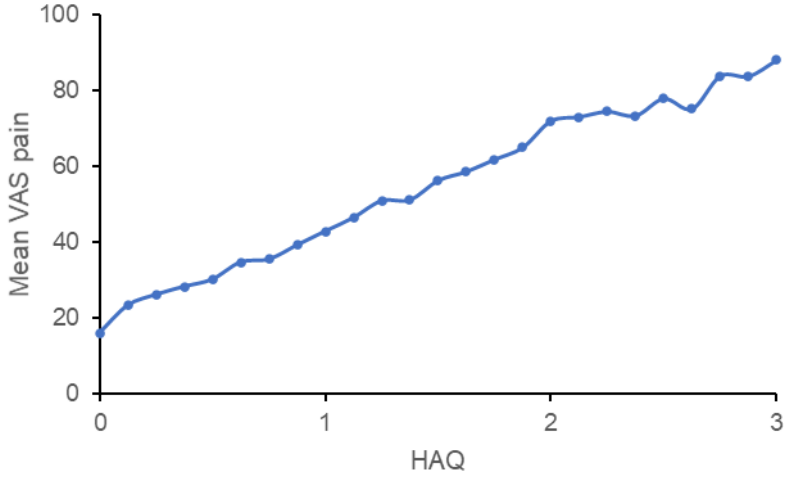
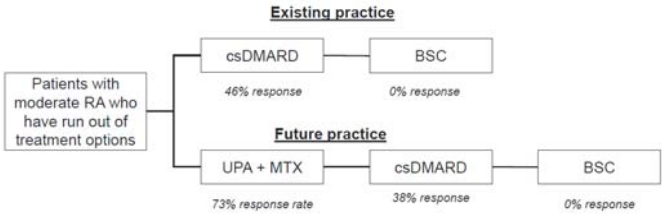
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			resulting, lower response rate for the upadacitinib model arm, compared with a 0% response rate for the best supportive care arm. The ERG explained that reducing the response rate for upadacitinib may underestimate the treatment cost in the model, compared with what would be expected in clinical practice" The approach advocated by AbbVie relates to the modelling of a circumstance where the placebo effect seen in clinical trials does not manifest in clinical practice and hence drug costs should likewise be lower since discontinuation rate will be higher (for efficacy rates diminished relative to their clinical trials). It would be methodologically unsound to separate treatment effects from costs. In response to issue 1 AbbVie provide an analysis in which a csDMARD used after two or more csDMARD failures in moderate RA is associated with a placebo related response rate and upadacitinib (and all other active drugs) manifest the efficacy seen in clinical trials (see Table 6). The other logically consistent approach is that if the effect seen in clinical trials is assumed not to manifest in clinical practice for any active drugs, then csDMARD after two or more csDMARD failures in moderate RA can be associated with a zero response rate and upadacitinib (and all other active drugs) manifest a reduced efficacy relative to that seen in their clinical trials. **Table 7: Methotrexate eligible patients AbbVie preferred approach (UPA + MTX) assuming placebo component of UPA + MTX efficacy does not manifest in clinical practice**  **ICERs** List prices for all drugs used except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies) £23,465 ***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;*	

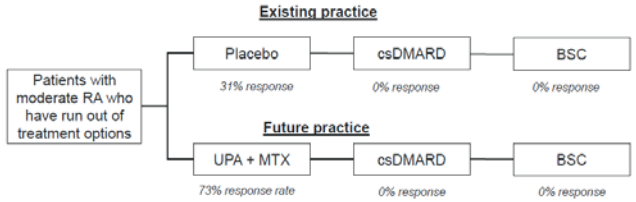
<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>Table 8: Methotrexate eligible patients assumed NICE preferred approach (UPA + MTX) assuming placebo component of UPA + MTX efficacy does not manifest in clinical practice
<table>
<tr><td> 
</td><td>ICERs</td></tr>
<tr><td>List prices used for all drugs except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)</td><td>£19,086</td></tr>
</table>
* in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;</td><td></td></tr>
<tr><td>24</td><td></td><td>AbbVie Ltd.</td><td><u>Section 3.15 does not adequately address the concerns expressed by AbbVie regarding using the mapping algorithm between HAQ and pain used in previous appraisals.</u>

The concern expressed by AbbVie in our technical engagement response (pages 25 and 26) that the use of the algorithm based on the National Databank for Rheumatic Diseases (NDB) as used in previous NICE appraisals provides the counterintuitive results that HAQ scores at the highest end of the spectrum (indicating lowest functionality) are associated with a reduction in pain is not addressed in the ACD. This is shown in Figure 3 reproduced from our technical response below.
Figure 3: HAQ-to-pain map based on using NDB (preferred by NICE)</td><td>Thank you for your comments.

A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.</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
			 The use of the SELECT trial-based algorithm does not show such a counterintuitive decrease in pain scores with HAQ scores at the highest end of the spectrum (Figure 4 Figure 4 reproduced from AbbVie technical engagement response below). Given this, AbbVie suggest that, at a minimum, ICER results using the SELECT trial-based algorithm should be presented alongside those using the NDB based one to bound the uncertainty around this parameter value. Furthermore, the committee states on page 18 that *"It concluded that the company's approach may be valid, but it preferred to use utilities calculated using the HAQ-to-pain mapping function used in the previous NICE technology appraisal, which was based on a much larger dataset".* It is worth noting that the SELECT trial-based algorithm is itself based upon a substantial dataset consisting of 3599 patients and 7963 observations. **Figure 4: HAQ-to-pain map based on SELECT trials. (AbbVie preferred approach)**	

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
			 Given this, AbbVie suggest that, at a minimum, ICER results using the SELECT trial-based algorithm should be presented alongside those using the NDB based one to bound the uncertainty around this parameter value. The ICERs presented below use both SELECT trial based and TA375 HAQ to pain mapping to estimate utilities to show the sensitivity of the ICERs to this assumption. **Table 9: Methotrexate eligible patients AbbVie preferred approach (UPA + MTX)**  **Utilities – TA375 approach**: £25,462 **Utilities – SELECT trial HAQ to pain map**: £21,601 List prices used for all drugs except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies) ***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line*	

<table>
<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>Table 10: Methotrexate eligible patients using NICE preferred approach (UPA + MTX) assuming placebo component of UPA + MTX efficacy manifests in clinical practice
<table>
<tr><td> 
</td><td>Utilities – TA375 approach</td><td>Utilities – SELECT trial HAQ to pain map</td></tr>
<tr><td>List prices for all drugs used except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)</td><td>£30,600</td><td>£24,183</td></tr>
</table>
* in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third</td><td></td></tr>
<tr><td>25</td><td></td><td>AbbVie Ltd.</td><td><u>The ACD incorrectly states the comparator and efficacy input in the AbbVie moderate RA base case.</u>

The ACD makes the following incorrect statement about the company’s base case after two or more conventional DMARDs:

“After two more conventional DMARDs, the company’s base case compared upadacitinib with best supportive care. In this analysis, best supportive care was assumed to give no EULAR response (0% response rate)” (page 15).

The cost effectiveness analysis approach discussed and the ICERs presented in the ACD in moderate RA relate entirely to upadacitinib combination therapy in methotrexate eligible patients. Given this, the description quoted above from page 15 should also refer to the AbbVie base case in methotrexate eligible patients. In the base case for methotrexate eligible patients in moderate RA after two or more csDMARD failure, the treatment sequence used in our submission was upadacitinib combination therapy or upadacitinib monotherapy then methotrexate (which is a csDMARD) then BSC VERSUS methotrexate then BSC (please refer to Figure 1 in relation to Issue 1). The response rate associated with methotrexate was 46% (the source of this efficacy was the csDMARD efficacy in the csDMARD-IR NMA). This information can be found on pages 132 and 141 of our original submission.

In the base case for methotrexate <u>ineligible</u> patients in moderate RA after two or more csDMARD failure the treatment sequence used in our submission was upadacitinib</td><td>Thank you, your comments have been noted.

A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.</td></tr>
</table>

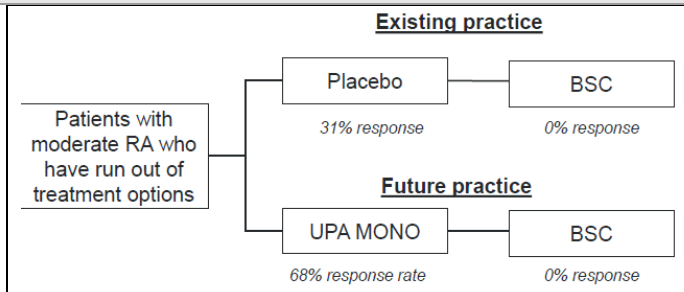
<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>monotherapy then BSC VERSUS BSC (with a 0% response rate associated with BSC). This information can be found on page 132 of our original submission. The final NICE scope for this appraisal specified BSC as a comparator in this position and therefore this treatment sequence met the requirements of the NICE scope for this appraisal.

The AbbVie base case compared to methotrexate (a csDMARD associated with a 46% response rate, followed by BSC associated with a 0% response rate). The approach advocated by the Committee assumes a 0% response rate for both csDMARD and BSC in the intervention and comparator arms but introduces a placebo response rate in the comparator arm instead, which is discussed in more detail in Issue 1.</td><td></td></tr>
<tr><td>26</td><td></td><td>AbbVie Ltd.</td><td><u>Given the issues addressed in Issue 1 and 2, AbbVie provide ICERs for upadacitinib monotherapy in methotrexate ineligible patients.</u>

Table 11: Methotrexate ineligible patients –AbbVie preferred approach (UPA MONOTHERAPY) assuming placebo component of upadacitinib monotherapy efficacy manifests in clinical practice
<table>
<tr><td><u>Existing practice</u>
Patients with moderate RA who have run out of treatment options
BSC
0% response
<u>Future practice</u>
UPA MONO
68% response rate
BSC
0% response</td><td>ICERs</td></tr>
<tr><td>List prices used for all drugs except upadacitinib plus 5% waning assumed* (base case transition to advanced therapies)</td><td>£17,288</td></tr>
</table>
* in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;

Table 12: Methotrexate ineligible patients – NICE assumed preferred approach (UPA MONOTHERAPY) assuming placebo component of upadacitinib monotherapy efficacy manifests in clinical practice</td><td>Thank you for your comments.

A second consultation is in progress following the second appraisal committee meeting. This will cover moderate rheumatoid arthritis.
.</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
				
			ICERs	
			List prices used for all drugs except upadacitinib plus 5% waning assumed* (base case transition to advanced therapies)	£33,158
			** in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;*	

NICE National Institute for Health and Care Excellence

Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]

Consultation on the appraisal consultation document – deadline for comments **5pm** on **21 February 2020.** 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 Ltd.
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:	Aysha Aslam

NICE National Institute for Health and Care Excellence

Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]

Consultation on the appraisal consultation document – deadline for comments **5pm** on **21 February 2020.** Email: NICE DOCS

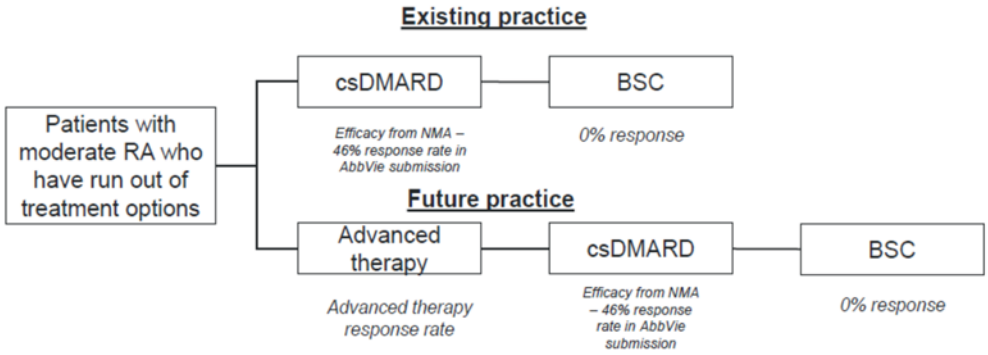
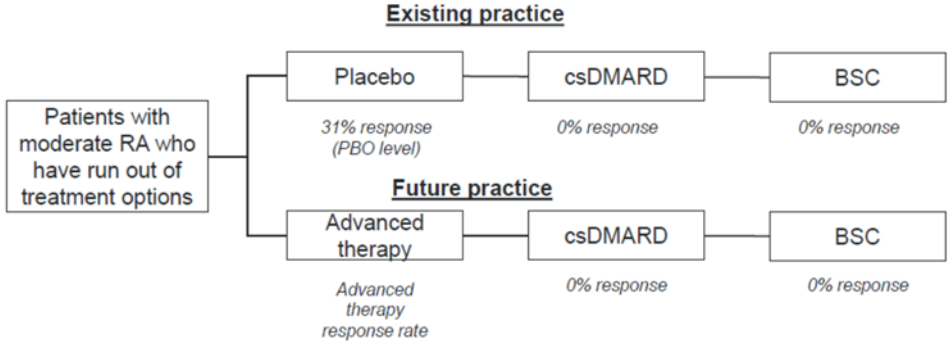
Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Summary	Thank you for the opportunity to comment on the appraisal consultation document (ACD) for upadacitinib for previously treated moderate to severe active rheumatoid arthritis (RA). We welcome the Committee's recommendation for the use of upadacitinib as an option for treating severe RA. We remain committed to resolving any remaining issues in moderate RA to enable patient access to upadacitinib in this area of extremely high unmet need. AbbVie believes that the changes to the modelling approach outlined in the ACD diverge from clinical practice, and from the precedents set in previous RA appraisals, including the previous multiple technology appraisal (TA375). Importantly, aligning with clinical practice and past precedent would lead to an **ICER of £25,111 in moderate RA rather than an ICER exceeding £30,000,** based on AbbVie's understanding of preferred assumptions within the ACD. Compared with the TA375 model, the AbbVie model provides broadly comparable ICERs. Using the AbbVie model to reproduce the analysis of adalimumab in moderate RA in TA375, the AbbVie model estimated an ICER of £55,866 compared to £51,472 reported in TA375. AbbVie acknowledge the comments outlined in the ACD around treatment waning and the number of patients transitioning from moderate to severe RA and suggest scenarios which address these issues. Healthcare professionals and patients have been waiting a long time for an advanced therapy to be available and funded in moderate RA. AbbVie is committed to working with NICE to enable immediate access to this oral therapy, which is the first JAK inhibitor to demonstrate statistically significantly better outcomes for patients compared to adalimumab plus methotrexate[1]. AbbVie has previously proposed a confidential discount that makes upadacitinib cost-effective in this population, based on the modelling approaches adopted in TA375 and precedents from subsequent appraisals. In order to ensure the fairness, objectivity and reasonableness of the upadacitinib appraisal, it is essential that the Committee continues to conduct its analysis in a manner consistent with the methodology used in previous appraisals for RA.

[1] Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Annals of the Rheumatic Diseases. Published Online First: 22 January 2020. doi: 10.1136/annrheumdis-2019-216655

NICE National Institute for Health and Care Excellence

Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]

Consultation on the appraisal consultation document – deadline for comments **5pm** on **21 February 2020.** Email: NICE DOCS

Issue 1: Inconsistency in the assumption of manifestation of placebo effect	**<u>The assumption that the upadacitinib response rate includes a placebo effect component whilst that of csDMARDs does not, substantially increases the ICER of upadacitinib in moderate RA and is inconsistent with clinical practice and the precedent set in previous appraisals</u>** To aid clarity, Figure 1 schematically represents the original approach submitted by AbbVie, which is aligned to TA375 and subsequent appraisals. Figure 2 represents the approach advocated by the committee as outlined in the ACD. **Figure 1 - Sequence A: Approach used in TA375 and the subsequent three NICE appraisals of RA drugs (baricitinib, tofacitinib and sarilumab) and in the AbbVie original submission**  **Figure 2 - Sequence B: Approach advocated by the committee in the ACD for upadacitinib in RA**  The ACD states that patients who have failed two or more csDMARDs would receive a csDMARD which at this stage is associated with a 0% response rate: *"The committee concluded that after 2 conventional DMARDs, previously used conventional DMARDs with optional corticosteroids would constitute best supportive care. This was the most appropriate comparator to upadacitinib because it reflected clinical practice. The committee also concluded that best supportive care was unlikely to give an EULAR response" (page 14).* In addition, it is assumed that the efficacy of upadacitinib is associated with a placebo related component and to account for this the ERG *"preferred to apply the placebo response from the NMA to BSC when it was compared with upadacitinib"* (page 15). The ERG's preferred source for this placebo response rate is the company's NMA which estimates a 31% response rate for placebo.

Please return to: **NICE DOCS**

Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]

Consultation on the appraisal consultation document – deadline for comments **5pm** on **21 February 2020.** Email: NICE DOCS

	AbbVie believes that the assumption of a placebo response component included in the efficacy of upadacitinib means that, to be consistent, a placebo response should similarly be assumed for csDMARD. This placebo response rate should be the same as that assumed for the upadacitinib arm, namely 31%. This 31% placebo response should be the "floor efficacy" that can be associated with csDMARD when it is used in patients who have tried and failed all other options; even if the drug has zero efficacy associated with its bioactive ingredients it would display a placebo effect. AbbVie continue to support the approach established in TA375 (and the three subsequent NICE RA appraisals) shown in Figure 1 which sources the efficacy of csDMARD in the comparator arm and in the intervention arm after the failure of the advanced therapy from the NMA. However, as a sensitivity analysis, (if a lower efficacy than that that estimated in the NMA is thought likely to be displayed in clinical practice) the "floor" for this efficacy should be "placebo effect" which in this appraisal has been estimated to be 31%, addressed in Table 6. AbbVie note that in the NICE preferred approach (Figure 2), a placebo has been included in the comparator arm. This is an artificial mechanism to net off placebo from the comparator arm and as such its inclusion does not reflect clinical practice.
Issue 2: Constraining the HE model to equalise treatment sequences does not model clinical practice	**<u>The ACD suggests that the relative effectiveness of active treatment is overestimated in treatment sequences of unequal lengths. Constraining sequences means all the benefits that will manifest in UK clinical practice are not captured adequately.</u>** The ACD states that treatment sequences of different length may bias the model in favour of the longer sequence. The rationale for equalising treatment sequences from the ACD is: *"The ERG advised that having unequal sequence lengths means at some point, an active treatment in the longer sequence is at the same position as best supportive care in the shorter sequence. The relative effectiveness of the active treatment at this point may be overestimated if best supportive care has no response rate" (page 14).* The ERG claim that by modelling the treatment sequences observed in clinical practice, the effectiveness of the intervention is *over*estimated is unsubstantiated by any evidence. In sequence A above (Figure 1), AbbVie believe the overestimation asserted by the Committee applies to a patient receiving a csDMARD after upadacitinib failure. To net off all this benefit, would be to negate the benefit of csDMARD in this position. The evidence for this approach has not been specified and means that the modelling would not reflect the benefits that will manifest in UK clinical practice. The ACD does not include a rationale of what is meant by an overestimation of an active treatment. This issue is explained in more detail in issue 3. The second reason expressed in the ACD by the Committee for equalising treatment sequences, is as follows: *"The clinical expert advised that in practice, any DMARD treatment would be expected to have a lower response rate the later it is used in the treatment pathway, compared with if it was used earlier. This was not captured in the network meta-analysis, which assumes a constant effect of each treatment regardless of its pathway position. So, the ERG explained it was likely that the model overestimated the response rate of treatments at later lines in the pathway. This means the cost-effectiveness model is further biased in favour of the arm with the longest treatment sequence (upadacitinib). The committee concluded that unequal treatment lengths may bias cost-effectiveness results" (page 14-15).*

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	This issue of waning of efficacy in later lines of therapy though can be addressed by applying a 5% waning of efficacy for third line use relative to second line and fourth line use relative to third line (second line efficacy is already lower than first line in the model results presented by the company in our technical engagement response because it sources values from the advanced therapy experienced NMA). The impact of this assumption upon ICERs is addressed in Table 4 to Table 6. This 5% waning rate is in line with the following estimation made by the clinical advisor quoted in the technical engagement report below. *"Regarding the magnitude of benefit a treatment provides at different lines in the treatment pathway, the clinical expert advised that bDMARDs are expected to give a lower response rate with each passing line of therapy (approximately 5% less each time)" (page 36 of the final technical report).*
Issue 3: Lack of explanation regarding "overestimation" of the active drug efficacy	**<u>The ACD provides a statement that an active drug when compared to BSC will result in an overestimation of the efficacy of the active drug as a rationale for equalising treatment sequences. It does not explain what it means by "overestimation"</u>** The ACD provides the following rationale for equalising treatment sequences between the intervention and comparator arms: *"The ERG advised that having unequal sequence lengths means at some point, an active treatment in the longer sequence is at the same position as best supportive care in the shorter sequence. The relative effectiveness of the active treatment at this point may be overestimated if best supportive care has no response rate" (page 14).* The modelling approach followed by AbbVie (aligned to TA375 and the subsequent three NICE RA drug appraisals) involves unequal treatment sequences between the intervention and comparator arms reflecting clinical practice. The ACD provides no explanation of what is meant by *"overestimated"* in this situation despite it being a rationale for rejecting past precedence. AbbVie note that Addendum 4 to the ERG Report provides a potential explanation for the Committee's approach where the ERG states: *"Suppose that all biologic trials the active intervention arm had a response rate of 35% while the sugar pill/control/placebo had a response rate of 30%. [New Paragraph] The company position is that the biologic warrants an NHS price wholly attributes the 35% response rate to the biologic. The ERG position warrants an NHS price that only attributes the net additional 5% response rate to the biologic."* (page 7 in section 2.4 titled How to net out control / placebo effectiveness) The implication of this statement is that the ERG believe that placebo effect should be netted off a new intervention because the NHS should not reimburse it and to not do so involves an "overestimation" of the efficacy of that new intervention. However, in the case of the unequal treatment sequences in the AbbVie preferred model (aligned to TA375 and reproduced in Figure 1, Issue 1) it is a csDMARD which is on the same line of therapy as BSC, and as such the "overestimation" relates to the efficacy of a csDMARD in this position. Since this is not the intervention under appraisal but is already reimbursed by the NHS, the ERG's rationale in Addendum 4 is no longer relevant.
Issue 4: Robustness of model in relation to	**<u>The ERG have failed to correct two of the four implementation errors they made to the health economic model.</u>** Correcting for all four implementation errors by the ERG shows that the ICERs using the AbbVie model are broadly comparable (using sequence 1 as the reference case) to ICERs

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ERG model validation

using TA375. This repeats the analysis carried out by the ERG in Addendum 4 of the ERG report in which only two of the four implementation errors are corrected and which concluded that *"The company model validation work of its addendum 3 appears to suggest that the company model is more favourable to the biologic sequences when comparing them with non-biologic containing sequences than the TA375 model"*.

The two additional errors are as follows:

- The incorrect implementation of efficacy values for all drugs (the ERG used the percentage of moderate responders in the TA375 model in cells in which total responders i.e. Moderate plus good responders were required)
- The use of INT_CON_DMARD, instead of the more appropriate option of TICORA, to simulate intensive csDMARD. INT_CON_DMARD is associated with a 0% discontinuation rate after the first six months unlike TICORA which is associated with discontinuation rate curves aligned to those used in TA 375 and the AbbVie model (and hence greater than zero for the life-time of the model)

As shown in Table 1 and Table 2 below correcting for all four implementation errors and repeating the analysis upon which the ERG's conclusion was made shows a close match for four of the seven ICERs between the models (2%-5% difference) with one ICER more favourable using the AbbVie model (by 17%) and two less favourable (by 17% and 40%). AbbVie provide more detail on this point in a document submitted as part of this ACD response.

Table 1: Comparison of AbbVie model output to TA375 model output correcting for all four implementation errors

	Using AbbVie model					ICERs (AbbVie model relative to TA375 model output)
	Costs	QALYs	Incremental costs (relative to SEQ 1)	Incremental QALYs (relative to SEQ 1)	ICERs	
Sequence 1	71,311	7.26				
Sequence 2	88,786	7.91	17,475	0.65	26,885	98%
Sequence 3	93,513	7.93	22,202	0.67	33,137	83%
Sequence 4	104,501	8.03	33,190	0.77	43,104	96%
Sequence 5	106,173	7.65	34,862	0.39	89,390	140%
Sequence 6	112,602	7.71	41,291	0.45	91,758	117%
Sequence 7	125,581	8.28	54,270	1.02	53,206	97%
Sequence 8	127,589	8.28	56,278	1.02	55,175	95%

Table 2: TA375 model output

	Using TA375 model				
	Costs	QALYs	Incremental costs (relative to SEQ 1)	Incremental QALYs (relative to SEQ 1)	ICERs
Sequence 1	73,841	7.25			
Sequence 2	90,596	7.86	16,755	0.61	27,467
Sequence 3	98,166	7.86	24,325	0.61	39,877
Sequence 4	111,463	8.09	37,622	0.84	44,788
Sequence 5	112,773	7.86	38,932	0.61	63,823
Sequence 6	124,989	7.9	51,148	0.65	78,689
Sequence 7	135,277	8.37	61,436	1.12	54,854
Sequence 8	138,894	8.37	65,053	1.12	58,083

Of relevance to this issue is the validation exercise submitted to NICE on the 8th November in which we reproduce the analysis of adalimumab in moderate RA carried out in TA375 using the AbbVie model. This showed the AbbVie model providing a less preferential ICER (£55,866) compared to that reported in TA375 (£51,472).

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Issue 5: Robustness of model relating to rate of transition from moderate to severe RA

The ACD states that AbbVie's health economic model is not robust because the rate of transition for moderate RA patients to severe RA advanced therapies in the model is lower than that observed in clinical practice. AbbVie present an additional analysis which addresses this issue.

In the ACD it is stated that that the cost effectiveness estimates for moderate RA are thought not to be robust because the rate of transition to severe RA advanced therapies in the health economic model is lower than that observed in clinical practice. While we remain confident in the validity of this estimate, the assumed rate has a negligible effect on the ICER. In the analysis presented in AbbVie's original ACD response which used discounted prices for adalimumab and assumed discounts for sarilumab and rituximab, using the extreme assumption of 87% of patients transitioning to severe RA only increases ICERs by 10% (list prices for all comparators are used in this version of our ACD response following a request from NICE on 18th August 2020)

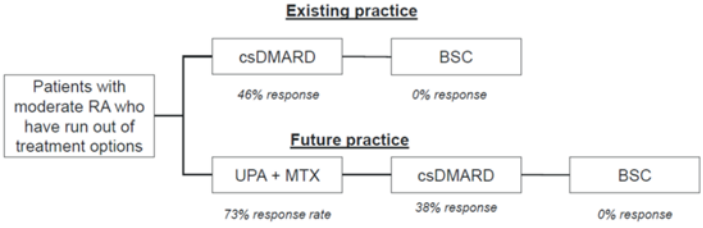
The percentage of patients transitioning to severe RA at two years in the comparator arm is about 19% if the transition rate is tripled compared to the baseline rate (by tripling the DAS 28 to HAQ ratio relative to baseline). The rate is similar to the ERAN database study consisting of newly diagnosed and csDMARD-treated patients. It should be noted that transition to severe RA in the model is linked to change in HAQ which in turn is assumed (based upon TA375 assumptions) to be the same in csDMARD treated and untreated patients. It is also worth noting that the HAQ curves based on Norton et al., are broadly linear in the first six years after which increases start to flatten out.

Table 3: Transition from moderate RA to severe RA advanced therapies (comparator arms for both NICE and AbbVie preferred approaches)

	Year 2	Maximum (by year 12)
Base case transition to advanced therapies	5%*	33%*
Double base case transition to advanced therapies	11%*	71%*
Triple base case transition to advanced therapies	19%*	87%*

** of surviving cohort*

Table 4: Methotrexate eligible patients AbbVie preferred approach (UPA + MTX)

	ICERs
	
Scenario 1: Using list prices for drugs other than upadacitinib	£25,110
Scenario 2: Assume no transition to severe RA advanced therapies	£29,557
Scenario 1 PLUS 5% waning assumed* (base case transition to advanced therapies)	£25,462
Scenario 1 plus 5% waning assumed* (double base case transition to advanced therapies)	£18,428
Scenario 1 plus 5% waning assumed* (triple base case transition to advanced therapies)	£13,492

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line*

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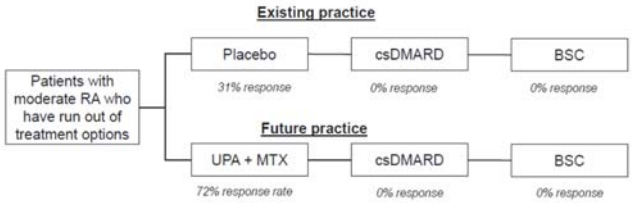
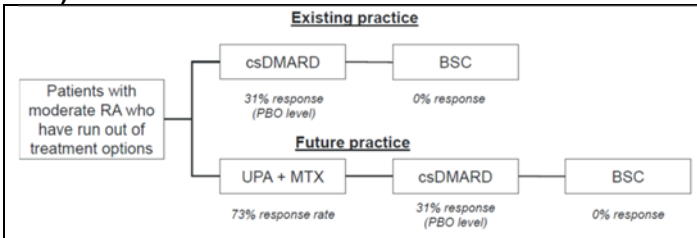
Table 5: Methotrexate eligible patients using NICE preferred approach (UPA + MTX)



	ICERs
Scenario 1: Using list prices for all drugs except upadacitinib	£29,501
Scenario 2: Assume no transition to severe RA advanced therapies	£33,320
Scenario 1 PLUS 5% waning assumed* (base case transition to advanced therapies)	£30,600
Scenario 1 plus 5% waning assumed* (double base case transition to advanced therapies)	£25,661
Scenario 1 plus 5% waning assumed* (triple base case transition to advanced therapies)	£21,773

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line*

Table 6: Methotrexate eligible patients AbbVie approach – sensitivity analysis placebo efficacy "floor" for assumed lower bound efficacy of csDMARD (UPA + MTX)



	ICERs
List prices for all drugs except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)	£20,501
List prices for all drugs except upadacitinib PLUS 5% waning assumed* (Double base case transition to advanced therapies)	£12,484
List prices for all drugs except upadacitinib PLUS 5% waning assumed* (Triple base case transition to advanced therapies)	£6,354

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line*

Issue 6: "Net treatment effect" approach

The ACD misrepresents the intention of the company's 'net treatment effect' approach

On page 16 of the ACD the following is stated:

"[Heading of section] The company's 'net treatment effect' analysis may be appropriate to model effectiveness of upadacitinib relative to best supportive care, but not the relative costs. [New Paragraph] 3.12: In its response to technical engagement, the company provided a scenario analysis which estimated the 'net treatment effect' of upadacitinib relative to the trial control arms. This decreased the upadacitinib response rate to reflect that some of the overall response could be because of a trial or placebo effect. In this analysis, the company used the resulting, lower response rate for the upadacitinib model arm, compared with a 0% response rate for the best supportive care arm. The ERG explained that reducing the response rate for upadacitinib may underestimate the treatment cost in the model, compared with what would be expected in clinical practice"

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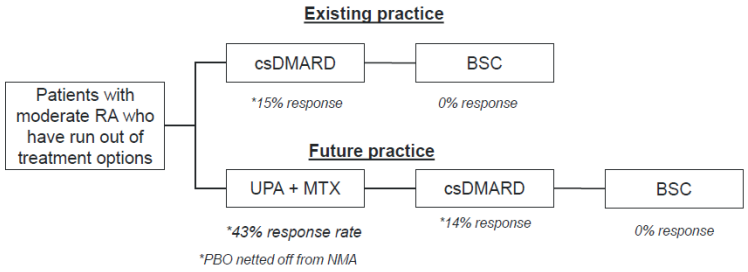
The approach advocated by AbbVie relates to the modelling of a circumstance where the placebo effect seen in clinical trials does not manifest in clinical practice and hence drug costs should likewise be lower since discontinuation rate will be higher (for efficacy rates diminished relative to their clinical trials). It would be methodologically unsound to separate treatment effects from costs.

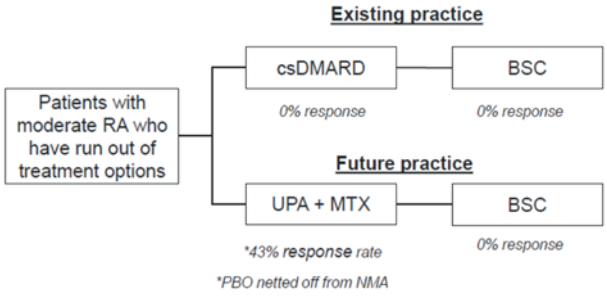
In response to issue 1 AbbVie provide an analysis in which a csDMARD used after two or more csDMARD failures in moderate RA is associated with a placebo related response rate and upadacitinib (and all other active drugs) manifest the efficacy seen in clinical trials (see Table 6). The other logically consistent approach is that if the effect seen in clinical trials is assumed not to manifest in clinical practice for any active drugs, then csDMARD after two or more csDMARD failures in moderate RA can be associated with a zero response rate and upadacitinib (and all other active drugs) manifest a reduced efficacy relative to that seen in their clinical trials.

Table 7: Methotrexate eligible patients AbbVie preferred approach (UPA + MTX) assuming placebo component of UPA + MTX efficacy does not manifest in clinical practice

	**ICERs**
List prices for all drugs used except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)	£23,465

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;*

Table 8: Methotrexate eligible patients assumed NICE preferred approach (UPA + MTX) assuming placebo component of UPA + MTX efficacy does not manifest in clinical practice

	**ICERs**
List prices used for all drugs except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)	£19,086

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;*

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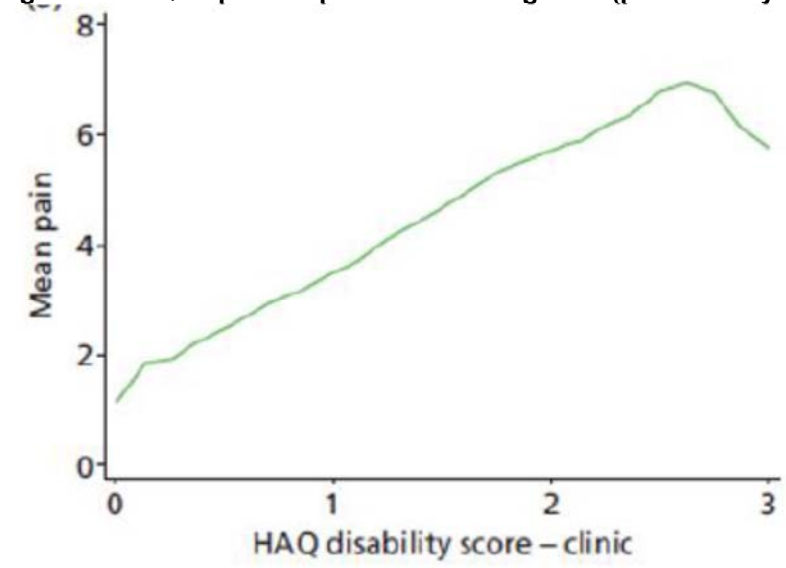
Issue 7: Mapping algorithm between HAQ and pain	**<u>Section 3.15 does not adequately address the concerns expressed by AbbVie regarding using the mapping algorithm between HAQ and pain used in previous appraisals.</u>** The concern expressed by AbbVie in our technical engagement response (pages 25 and 26) that the use of the algorithm based on the National Databank for Rheumatic Diseases (NDB) as used in previous NICE appraisals provides the counterintuitive results that HAQ scores at the highest end of the spectrum (indicating lowest functionality) are associated with a reduction in pain is not addressed in the ACD. This is shown in Figure 3 reproduced from our technical response below. **Figure 3: HAQ-to-pain map based on using NDB (preferred by NICE)**  The use of the SELECT trial-based algorithm does not show such a counterintuitive decrease in pain scores with HAQ scores at the highest end of the spectrum (Figure 4 Figure 4 reproduced from AbbVie technical engagement response below). Given this, AbbVie suggest that, at a minimum, ICER results using the SELECT trial-based algorithm should be presented alongside those using the NDB based one to bound the uncertainty around this parameter value. Furthermore, the committee states on page 18 that *"It concluded that the company's approach may be valid, but it preferred to use utilities calculated using the HAQ-to-pain mapping function used in the previous NICE technology appraisal, which was based on a much larger dataset".* It is worth noting that the SELECT trial-based algorithm is itself based upon a substantial dataset consisting of 3599 patients and 7963 observations.

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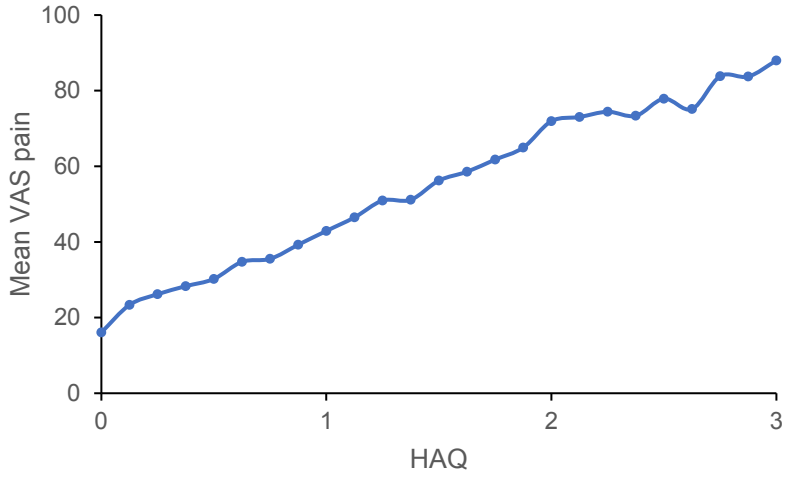
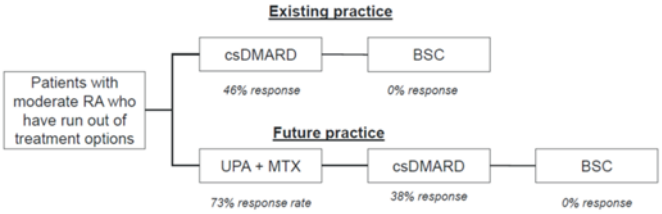
Figure 4: HAQ-to-pain map based on SELECT trials. (AbbVie preferred approach)



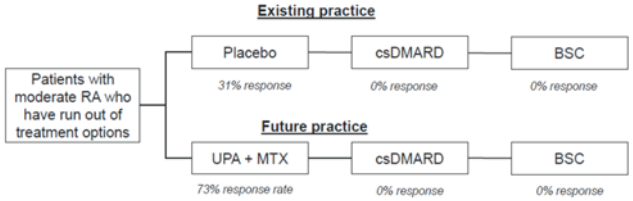
Given this, AbbVie suggest that, at a minimum, ICER results using the SELECT trial-based algorithm should be presented alongside those using the NDB based one to bound the uncertainty around this parameter value. The ICERs presented below use both SELECT trial based and TA375 HAQ to pain mapping to estimate utilities to show the sensitivity of the ICERs to this assumption.

Table 9: Methotrexate eligible patients AbbVie preferred approach (UPA + MTX)

	Utilities – TA375 approach	**Utilities – SELECT trial HAQ to pain map**
		
List prices used for all drugs except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)	£25,462	£21,601

** in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line*

Table 10: Methotrexate eligible patients using NICE preferred approach (UPA + MTX) assuming placebo component of UPA + MTX efficacy manifests in clinical practice

	Utilities – TA375 approach	**Utilities – SELECT trial HAQ to pain map**
		
List prices for all drugs used except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)	£30,600	£24,183

** in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third*

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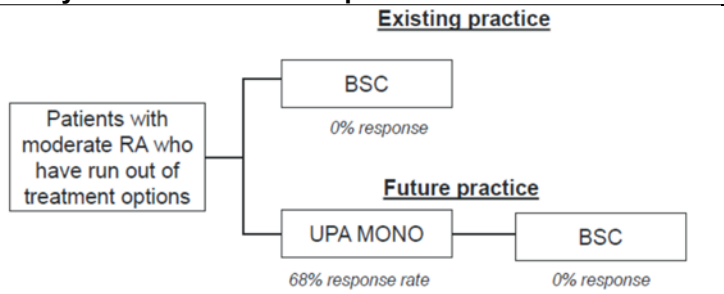
Issue 8: Incorrect assumptions pertaining to AbbVie's base case.	**The ACD incorrectly states the comparator and efficacy input in the AbbVie moderate RA base case.** The ACD makes the following incorrect statement about the company's base case after two or more conventional DMARDs: *"After two more conventional DMARDs, the company's base case compared upadacitinib with best supportive care. In this analysis, best supportive care was assumed to give no EULAR response (0% response rate)" (page 15).* The cost effectiveness analysis approach discussed and the ICERs presented in the ACD in moderate RA relate entirely to upadacitinib combination therapy in methotrexate eligible patients. Given this, the description quoted above from page 15 should also refer to the AbbVie base case in methotrexate eligible patients. In the base case for methotrexate eligible patients in moderate RA after two or more csDMARD failure, the treatment sequence used in our submission was upadacitinib combination therapy or upadacitinib monotherapy then methotrexate (which is a csDMARD) then BSC VERSUS methotrexate then BSC (please refer to Figure 1 in relation to Issue 1). The response rate associated with methotrexate was 46% (the source of this efficacy was the csDMARD efficacy in the csDMARD-IR NMA). This information can be found on pages 132 and 141 of our original submission. In the base case for methotrexate ineligible patients in moderate RA after two or more csDMARD failure the treatment sequence used in our submission was upadacitinib monotherapy then BSC VERSUS BSC (with a 0% response rate associated with BSC). This information can be found on page 132 of our original submission. The final NICE scope for this appraisal specified BSC as a comparator in this position and therefore this treatment sequence met the requirements of the NICE scope for this appraisal. The AbbVie base case compared to methotrexate (a csDMARD associated with a 46% response rate, followed by BSC associated with a 0% response rate). The approach advocated by the Committee assumes a 0% response rate for both csDMARD and BSC in the intervention and comparator arms but introduces a placebo response rate in the comparator arm instead, which is discussed in more detail in Issue 1.
Issue 9: ICERs for upadacitinib monotherapy in methotrexate ineligible patients.	**Given the issues addressed in Issue 1 and 2, AbbVie provide ICERs for upadacitinib monotherapy in methotrexate ineligible patients.** **Table 11: Methotrexate ineligible patients –AbbVie preferred approach (UPA MONOTHERAPY) assuming placebo component of upadacitinib monotherapy efficacy manifests in clinical practice**

	**ICERs**
List prices used for all drugs except upadacitinib plus 5% waning assumed* (base case transition to advanced therapies)	£17,288

** in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;*

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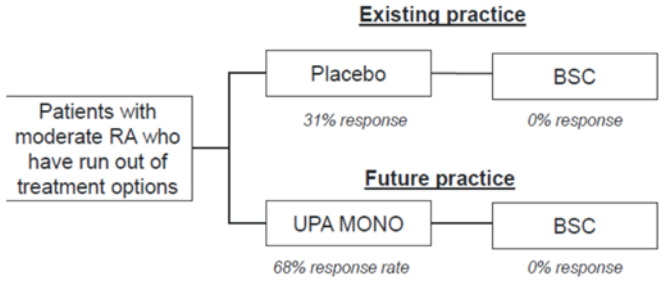
Table 12: Methotrexate ineligible patients – NICE assumed preferred approach (UPA MONOTHERAPY) assuming placebo component of upadacitinib monotherapy efficacy manifests in clinical practice



	ICERs
List prices used for all drugs except upadacitinib plus 5% waning assumed* (base case transition to advanced therapies)	£33,158

** in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;*

Insert extra rows as needed

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- Do not use abbreviations
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Appraisal Consultation Document: Tables and figures included in AbbVie response

Upadacitinib for treating moderate to severe rheumatoid arthritis

ID1400

Issue 1

Figure 1: Sequence A: Approach used in TA375 and the subsequent three NICE appraisals of RA drugs (baricitinib, tofacitinib and sarilumab) and in the AbbVie original submission

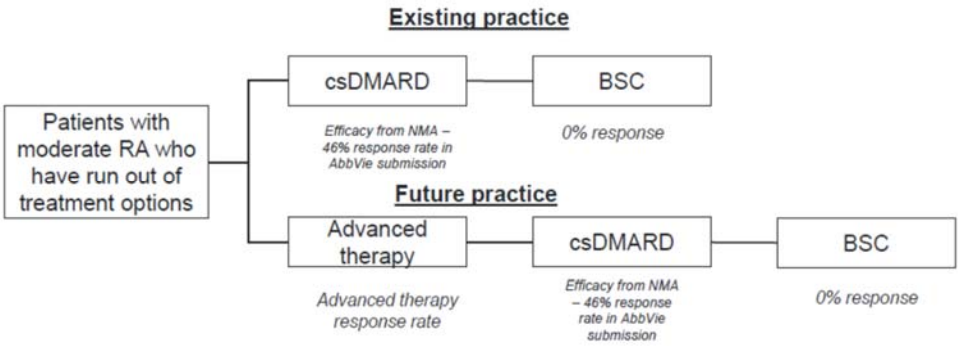
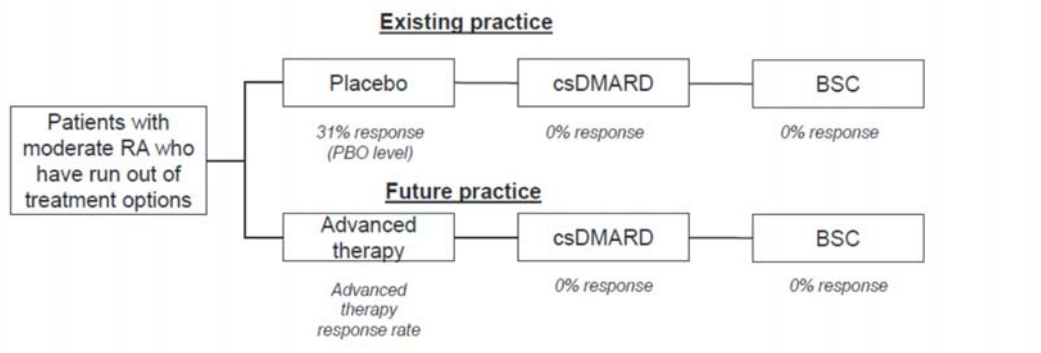


Figure 2: Sequence B: Approach advocated by the committee in the ACD for upadacitinib in RA



Issue 4

Table 1: Comparison of AbbVie model output to TA375 model output correcting for all four implementation errors

Using AbbVie model						ICERs (AbbVie model relative to TA375 model output)
	Costs	QALYs	Incremental costs (relative to SEQ 1)	Incremental QALYs (relative to SEQ 1)	ICERs	
Sequence 1	71,311	7.26				
Sequence 2	88,786	7.91	17,475	0.65	26,885	98%
Sequence 3	93,513	7.93	22,202	0.67	33,137	83%
Sequence 4	104,501	8.03	33,190	0.77	43,104	96%
Sequence 5	106,173	7.65	34,862	0.39	89,390	140%
Sequence 6	112,602	7.71	41,291	0.45	91,758	117%
Sequence 7	125,581	8.28	54,270	1.02	53,206	97%
Sequence 8	127,589	8.28	56,278	1.02	55,175	95%

Table 2: TA375 model output

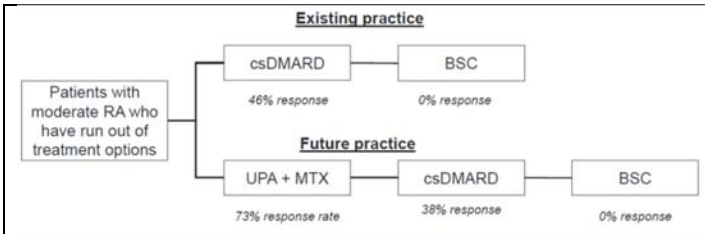
Using TA375 model					
	Costs	QALYs	Incremental costs (relative to SEQ 1)	Incremental QALYs (relative to SEQ 1)	ICERs
Sequence 1	73,841	7.25			
Sequence 2	90,596	7.86	16,755	0.61	27,467
Sequence 3	98,166	7.86	24,325	0.61	39,877
Sequence 4	111,463	8.09	37,622	0.84	44,788
Sequence 5	112,773	7.86	38,932	0.61	63,823
Sequence 6	124,989	7.9	51,148	0.65	78,689
Sequence 7	135,277	8.37	61,436	1.12	54,854
Sequence 8	138,894	8.37	65,053	1.12	58,083

Issue 5

Table 3: Transition from moderate RA to severe RA advanced therapies (comparator arms for both NICE and AbbVie preferred approaches)

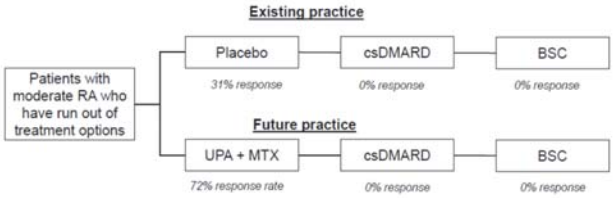
	Year 2	Maximum (by year 12)
Base case transition to advanced therapies	5%*	33%*
Double base case transition to advanced therapies	11%*	71%*
Triple base case transition to advanced therapies	19%*	87%*

Table 4: Methotrexate eligible patients AbbVie preferred approach (UPA + MTX)

	ICERs
	
Scenario 1: Using list prices for drugs other than upadacitinib	£25,110
Scenario 2: Assume no transition to severe RA advanced therapies	£29,557
Scenario 1 PLUS 5% waning assumed* (base case transition to advanced therapies)	£25,462
Scenario 1 plus 5% waning assumed* (double base case transition to advanced therapies)	£18,428
Scenario 1 plus 5% waning assumed* (triple base case transition to advanced therapies)	£13,492

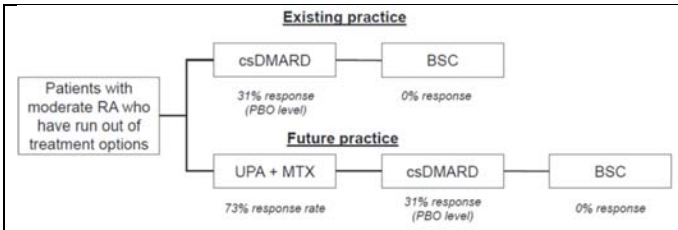
***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line*

Table 5: Methotrexate eligible patients using NICE preferred approach (UPA + MTX)

	**ICERs**
Scenario 1: Using list prices for all drugs except upadacitinib	£29,501
Scenario 2: Assume no transition to severe RA advanced therapies	£33,320
Scenario 1 PLUS 5% waning assumed* (base case transition to advanced therapies)	£30,600
Scenario 1 plus 5% waning assumed* (double base case transition to advanced therapies)	£25,661
Scenario 1 plus 5% waning assumed* (triple base case transition to advanced therapies)	£21,773

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line*

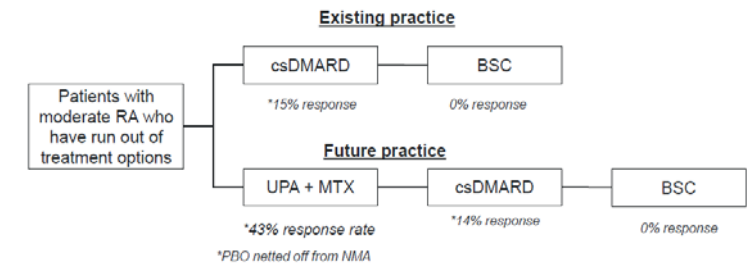
Table 6: Methotrexate eligible patients AbbVie approach – sensitivity analysis placebo efficacy "floor" for assumed lower bound efficacy of csDMARD (UPA + MTX)

	**ICERs**
List prices for all drugs except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)	£20,501
List prices for all drugs except upadacitinib PLUS 5% waning assumed* (Double base case transition to advanced therapies)	£12,484
List prices for all drugs except upadacitinib PLUS 5% waning assumed* (Triple base case transition to advanced therapies)	£6,354

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line*

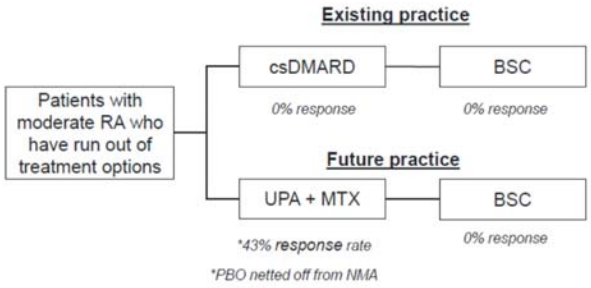
Issue 6

Table 7: Methotrexate eligible patients AbbVie preferred approach (UPA + MTX) assuming placebo component of UPA + MTX efficacy does not manifest in clinical practice

	**ICERs**
List prices for all drugs used except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)	£23,465

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;*

Table 8: Methotrexate eligible patients assumed NICE preferred approach (UPA + MTX) assuming placebo component of UPA + MTX efficacy does not manifest in clinical practice

	**ICERs**
List prices used for all drugs except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)	£19,086

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;*

Issue 7

Figure 3: HAQ-to-pain map based on using NDB (preferred by NICE)

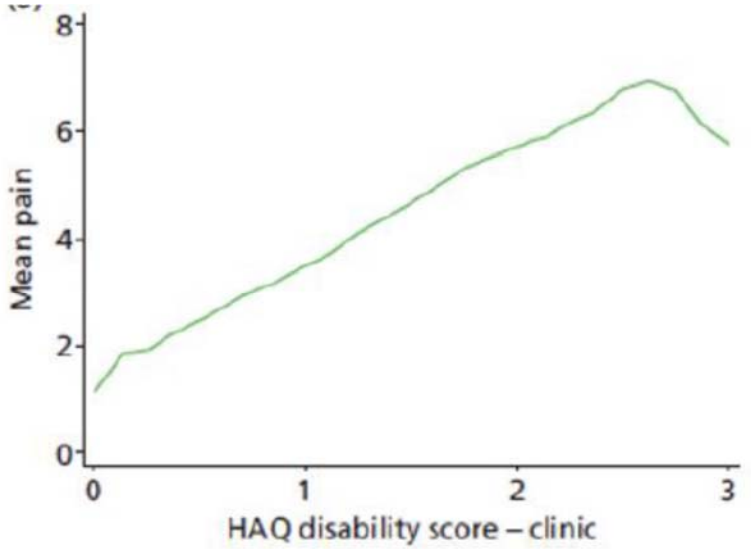


Figure 4: HAQ-to-pain map based on SELECT trials. (AbbVie preferred approach)

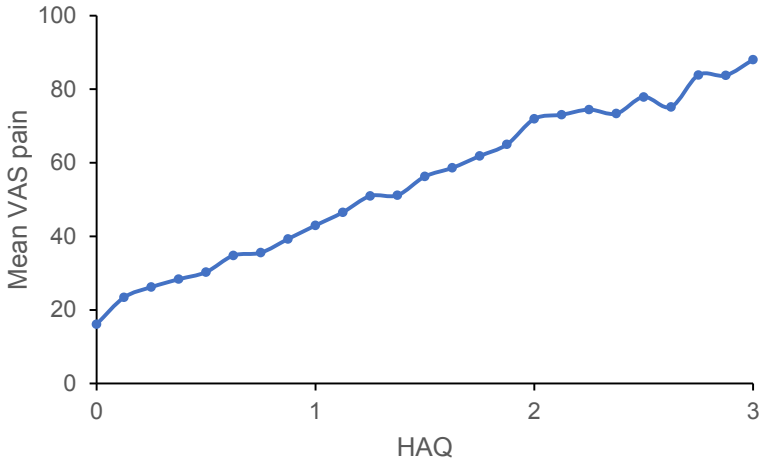
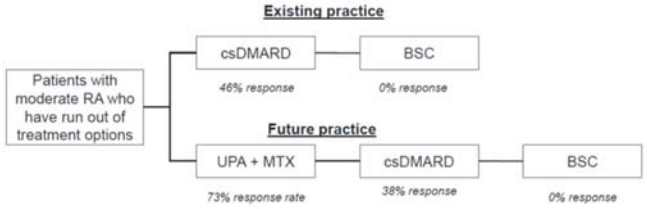
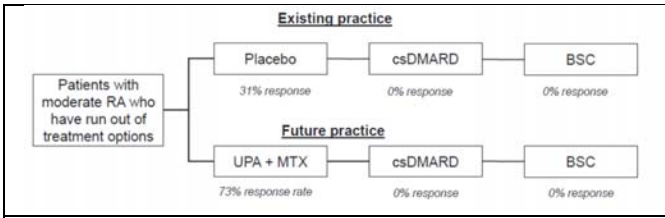


Table 9: Methotrexate eligible patients AbbVie preferred approach (UPA + MTX)

	**Utilities – TA375 approach**	**Utilities – SELECT trial HAQ to pain map**
List prices used for all drugs except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)	£25,462	£21,601

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line*

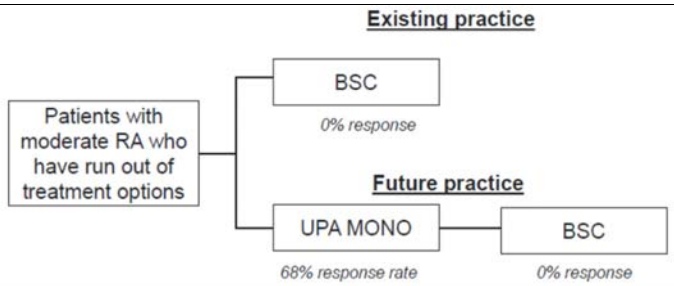
Table 10: Methotrexate eligible patients using NICE preferred approach (UPA + MTX) assuming placebo component of UPA + MTX efficacy manifests in clinical practice

	**Utilities – TA375 approach**	**Utilities – SELECT trial HAQ to pain map**
List prices for all drugs used except upadacitinib PLUS 5% waning assumed* (base case transition to advanced therapies)	£30,600	£24,183

***** *in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third*

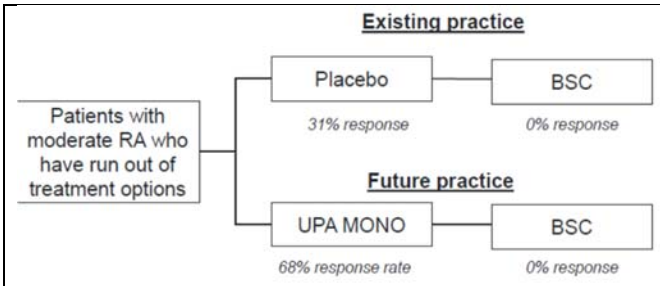
Issue 9

Table 11: Methotrexate ineligible patients –AbbVie preferred approach (UPA MONOTHERAPY) assuming placebo component of upadacitinib monotherapy efficacy manifests in clinical practice

	**ICERs**
List prices used for all drugs except upadacitinib plus 5% waning assumed* (base case transition to advanced therapies)	£17,288

** in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;*

Table 12: Methotrexate ineligible patients – NICE assumed preferred approach (UPA MONOTHERAPY) assuming placebo component of upadacitinib monotherapy efficacy manifests in clinical practice

	**ICERs**
List prices used for all drugs except upadacitinib plus 5% waning assumed* (base case transition to advanced therapies)	£33,158

** in the efficacy of a drug positioned third line treatment relative to a second line and fourth line relative to third line;*

NICE National Institute for Health and Care Excellence

Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]

Consultation on the appraisal consultation document – deadline for comments **5pm** on **21 February 2020.** 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):	British Society for Rheumatology
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Honorarium for attending advisory board for JAK inhibitors in development for RA: Abbvie and Gilead Honorarium for speaking at medical meetings: Biogen and UCB
Name of commentator person completing form:	[redacted]

Comment number	**Comments**

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	Insert each comment in a new row. 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	We are grateful for the opportunity of responding to the ACD on upadacitinib in rheumatoid arthritis and are pleased that NICE have recommended treatment for patients with severe disease. However, we are disappointed that NICE have failed to approve effective treatment for patients with moderate disease ie those with a disease activity score between 3.2 and 5.1. This group of patients have significant symptoms and progressive disability and yet if they fail disease modifying anti-rheumatic drugs they do not have any other available treatment other than best supportive care. Clinical trial data with upadacitinib has shown this treatment to be effective in both severe and moderate rheumatoid arthritis. Trials have demonstrated efficacy with upadacitinib that is at least as effective as adalimumab: ACD p10 *"The trials show upadacitinib is more clinically effective than adalimumab, conventional DMARDs (including methotrexate) or placebo for moderate to severe disease that has responded inadequately to conventional DMARDs."* Following TA 375 Stevenson and colleagues from ScHARR stated "Exploratory analyses indicate that if the price of bDMARD (excluding RTX) were reduced by 50%, the mean ICER would decline to £24,500 for patients with severe RA and £31,500 for patients with moderate to severe RA." (*Stevenson M et al J Rheum 2017; 44:973-80*). The price of [redacted] is less than [redacted] of the cost adalimumab in the TA375 analysis and at least as effective. Its place in the treatment pathway is similar. It is inconceivable that it is not cost-effective in moderate rheumatoid arthritis if the same methodology used in TA 375 is undertaken. We consider the approach taken by the ERG to lead to this negative recommendation for moderate rheumatoid arthritis is flawed and is different to all previous appraisals at least in rheumatology. As such it is our view that if the ACD is not revised that NICE would be failing to act fairly in the evaluation of this technology. 3.11 p15 "*The ERG advised that some proportion of the upadacitinib response seen in the clinical trials would be caused by the same placebo effect seen in the control arms. The ERG therefore preferred to apply the placebo response from the network meta-analysis to best supportive care when it was compared with upadacitinib. The committee recalled that the clinical expert would not expect best supportive care to give a treatment response at this position. However, it agreed that the placebo effect will be present in the upadacitinib response rates. Therefore, comparing this with a 0% response rate would overestimate the effectiveness of upadacitinib relative to best supportive care. The committee concluded that it was not appropriate to apply a 0% response rate for best supportive care while also applying the full, observed response rate for upadacitinib.*"

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	We consider this is an unsupported supposition by the ERG not based on published evidence. It is beyond logic to consider that a patient not receiving any new treatment and being treated with best supportive care would have a placebo response. This implies that, for example, a patient may fail to achieve remission or low disease state with methotrexate would have treatment withdrawn and then recommenced and have a better response because of a placebo response. In clinical practice disease modifying anti-rheumatic drugs are usually continued in moderate rheumatoid arthritis, not stopped and restarted. NICE guidelines are to use combination therapies in a step up approach and to step down only if the target of remission or low disease state (NG100 1.4.3). In those with moderate disease there is no indication to withdraw then recommence treatment. We recommend that the ERG revise their recommendation and undertake an analysis that reflects the reality of treatment.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or 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.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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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 Ltd
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] – National Market Access and Health Economics

Comment number	Comments
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Section 3.2	The ACD classifies tofacitinib and baricitinib as biologic DMARDS, when this is not the case based on treatment pathway guidelines from NICE (source: https://pathways.nice.org.uk/pathways/rheumatoid-arthritis#path=view%3A/pathways/rheumatoid-arthritis/drug-treatment-for-rheumatoid-arthritis.xml&content=view-node%3Anodes-inadequate-response-or-intolerance-to-biological-dmards-and-rituximab-is-not-suitable). UCB believes that should categorise these two treatments differently within the ACD document.
Section 3.7	UCB believes that the does not provide enough evidence for decision-making in moderate population e.g. number of treatment failures. There is no consistent outcome in terms of treatment effect as the number of treatment failures increases. This contradicts with company's common effects NMA assumption in the treatment pathway. Overall, this may impact the cost-effectiveness results.
Section 3.9	UCB believes that the appropriate comparator for the moderate disease after 2 conventional DMARDs is best supportive care, which is unlikely to give an EULAR response.
Section 3.10	UCB believes that comparing treatment sequences of different lengths may result in a misleading result.
Section 3.12	UCB believes that "net treatment effect" is misleading as this analysis does not include other factors who may have an impact on the model e.g. natural recovery. UCB agrees with ERG that the response rate for upadacitinib may underestimate the treatment cost in the model, compared with what would be expected in clinical practice
Section 3.13	UCB recommends that HAQ trajectories should be considered as these have been incorporated for both UPA and BSC responders.
Section 3.14	UCB believes that the company underpredict the transition rate from moderate to severe in their base scenario concerning based on the literature (Kiely et al). This underprediction has a clear impact on the cost-effectiveness results in favour of UPA.
Section 3.15	UCB believes that larger datasets provide a more confident and robust source of information thus TA375 is preferred.
Section 3.17	UCB believes that there is no consistency with TA375 in how the moderate sub-group has been modelled. That it would be useful for the ACD to provide this context as this may add further uncertainty to the submitted CE analysis for the moderate population which may have an impact on the final ICER acceptable range.

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Recommendation section	UCB believes that for consistency, the ACD should not include language along the lines of what was included in the CZP PsO guidance. As immunology is a crowded space and if NICE included that statement for CZP in PsO then UCB believes that this should be applicable in Ra space as well. Upadacitinib rec: *"It recommends treatment should start with the least expensive drug (taking into account administration costs, dose needed and product price per dose) and should only be continued according to European League Against Rheumatism (EULAR) response at 6 months."* CZP (PsO) rec: *"If patients and their clinicians consider certolizumab pegol to be one of a range of suitable treatments, the least expensive should be chosen (taking into account administration costs, dosage, price per dose andcommercial arrangements)"*

Insert extra rows as needed

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Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]

ERG Review of Company's Response to ACD

21 August 2020

Produced by

Peninsula Technology Assessment Group (PenTAG)
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1. SUMMARY

Rather than present results for patients at different points in the treatment pathway, the company models a less well defined "Patients with moderate RA who have run out of treatment options". The company prefers to not net out the placebo effect, possibly as it notes that "It would be methodologically unsound to separate treatment effects from costs".

The company prefers to adopt one of two approaches:

1. Apply the full placebo inclusive treatment effect for 1st line upadacitinib but 0% response rates for 1st line in the comparator arm.
2. Apply the full placebo inclusive treatment effects for both 1st line upadacitinib and 1st line active treatment, typically MTX, in the comparator arm, but follow these with a 2nd line treatment in the upadacitinib arm with the placebo effect but a 2nd line treatment in the comparator arm with 0% response rates.

In short, the company thinks that the placebo effect should be applied one more time in the upadacitinib arm than in the comparator arm.

The ERG thinks that the second approach of the company does not consider the possibility that the 1st line active treatment in the comparator arm could be followed by 2nd line upadacitinib. If this is considered, the treatment sequence with upadacitinib at 1st line has a very poor cost effectiveness compared to conventional willingness to pay thresholds.

The company presents one cost effectiveness estimate that nets out the company NMA placebo effect from the upadacitinib effectiveness estimates. It results in a cost effectiveness estimate of £19,086 per QALY for the methotrexate eligible, when the upadacitinib PAS and is applied.

The company introduces treatment waning by line of treatment. This has little effect upon results. Waning is assumed to be a 5% proportionate reduction in response by line; i.e. a 1st line overall response of 40% would be reduced at 2nd line to 38%. It is not clear whether the NICE TC document intended the 5% to be a proportionate or an absolute reduction.

The company introduces accelerated progression to severe RA. It notes that tripling the HAQ to DAS28 coefficient estimated by the company from SELECT trial data results in [redacted] of patients in the comparator arm progressing to severe RA by year 2, in line with ERAN data. By year 12 this implies [redacted] have progressed to severe RA.

The ERG presents two approaches:

1. Retaining the placebo effect.
2. Netting out the placebo effect from both upadacitinib and from the comparator arm.

The ERG thinks that the placebo effect should be applied the same number of times in both arms.

The ACD specifies that BSC is the appropriate comparator. It can be argued that this means that the head to head results of the SELECT trials should be applied. Using the head to head results is also aligned with section 5.2.12 of the NICE methods guide. The head to head results of the SELECT trials suggest a smaller benefit from upadacitinib over placebo than the company NMA. They worsen the cost effectiveness estimate for upadacitinib. SELECT-MONOTHERAPY had an active control of methotrexate. Consequently, the cost effectiveness estimates that apply the head to head results of SELECT-MONOTHERAPY should perhaps be better viewed as for upadacitinib relative to csDMARD.

The ERG presents additional analyses which assume that upadacitinib use for moderate RA can affect the treatments patients are likely to receive when they progress to severe RA.

2. MAIN POINTS OF ACD: COMPANY RESPONSE & ERG COMMENTS

For the economic modelling among moderate RA patients the ERG summarises the main points of the ACD and the company response to these points, followed by a brief ERG comment. These aspects are explored in more detail in later sections.

ACD Section 3.3: For moderate RA there are two positions under consideration: among patients who have not responded to 1 csDMARD and among patients who have not responded to ≥ 2 csDMARDs. For the latter there are two possible comparators: csDMARDs or BSC

- **Company ACD response:**

  The company moves away from explicitly labelled consideration of position 1 and position 2 to a more ambiguously labelled consideration of upadacitinib among moderate RA patients "who have run out of treatment options".

- **ERG comment:**

  The ERG thinks that much of the company analyses relate to position 1 when patients can still meaningfully intensify their csDMARDs. These analyses fail to consider the cost effectiveness of patients intensifying their csDMARDs before going on to upadacitinib compared to trying upadacitinib before intensifying their csDMARDs.

ACD Section 3.4: The SELECT trials were relevant and acceptable for decision making but did not include all relevant comparators.

- **Company ACD response:**

  None.

- **ERG comment**:

  Given ACD sections 3.8 and 3.9 and section 5.2.12 of the NICE methods guide, when considering upadacitinib treatment for moderate RA patients the SELECT trials' head to head results may be the relevant comparison. The company NMAs may only be required for modelling severe RA patients.

ACD Section 3.8: For moderate RA the preferred position is among patients who have not responded to ≥ 2 csDMARDs. UPA+MTX is preferable to UPA monotherapy among patients who tolerate MTX.

- **Company ACD response**:

  The company moves away from explicitly labelled consideration of position 1 and position 2 to a more ambiguously labelled consideration of upadacitinib among moderate RA patients.

  The company also appears to only consider MTX, labelled csDMARD in its diagrams, and placebo/BSC as comparators. It appears that it does not consider intensified csDMARDs.

- **ERG comment**:

  The ERG interpretation of ACD Section 3.3 is that upadacitinib for moderate RA should be evaluated when patients have reached the end of the line of csDMARD intensification. This interpretation is further supported by ACD Section 3.9.

  While UPA+MTX is preferable to UPA monotherapy among those who can tolerate MTX, the assessment of the overall cost effectiveness of upadacitinib should bear in mind the cost effectiveness of UPA monotherapy among those who cannot tolerate MTX.

ACD Section 3.9: For patients who have not responded to ≥ 2 csDMARDs the comparator should be BSC.

- **Company ACD response**:

  The company mainly considers csDMARD, MTX, as the comparator, with it also being possible to receive 2nd line csDMARD after 1st line upadacitinib.

  The company provides some analyses comparing upadacitinib with placebo / BSC.

- **ERG comment**:

  The CS only presents the treatment sequences it models for those with moderate RA. It does not present the treatment sequences that are assumed for those who have transitioned to severe RA. These patients are assumed to receive ADA+MTX followed by RTX+MTX followed by SRL+MTX followed by BSC. This is as per the ERG base case sequences for those who can receive MTX.

The ERG also provided scenario analyses which applied alternative treatment sequences for those transitioning to severe RA, exploring the possibility that after failure of one treatment clinicians might prefer not to use another with the same or a similar method of action.

ACD Section 3.10: Treatment sequences of different length may bias the analysis if it leads to the longer treatment sequence having a greater placebo effect applied than the shorter treatment sequence.

- **Company ACD response**:

  As in its original submission the company retains treatment sequences of different length which apply the placebo effect more time in the upadacitinib arm than in the comparator arm.

- **ERG comment**:

  None, beyond those already made in the ERG report.

ACD Section 3.11: It is not appropriate to assume the trial/NMA response rate estimates for active comparators but 0% response for BSC where BSC is the comparator. The placebo effect will be present in the active treatments' response rate estimates.

- **Company ACD response**:

  The company preferred approach of Table 4 moves the comparison of an active comparator with BSC to 2nd line treatment. This retains the placebo effect for the active treatment but sets the response rate for BSC to 0%.

- **ERG comment**:

  None, beyond those already made in the ERG report.

ACD Section 3.12: The company TC response approach to netting out response rates may be appropriate for estimating patient gains. But it is likely to underestimate the net costs.

- **Company ACD response**:

  The company 21 Nov 2019 TC response argued for net treatment effects which in effect subtracted the placebo/BSC response rates from those of the upadacitinib response rates: TC response Issue 2 page 4: "The appropriate methodological approach would be to net off the inflated efficacy of upadacitinib directly from the upadacitinib" and in more detail in table 3 on page 8.

The company ACD response largely abandons this method in its ACD response, though Table 8 retains it.

- **ERG comment**:

  The ERG will present ICERs applying the company TC response approach to netting out placebo effects.

  Given the ACD concerns around net costs, the ERG will also present the corresponding analyses which apply treatment effects inclusive of placebo effects.

ACD Section 3.13: Applying the HAQ progression for those on bDMARDs to those on BSC is likely to optimistic for BSC. It is appropriate to model a different HAQ progression for those on bDMARDs than that of those on BSC. Patients modelled as responding to BSC should have the same HAQ trajectory as TA375 responders to csDMARDs.

- **Company ACD response**:

  The company applies the TA375 base case assumptions, subsequent to an initial HAQ improvement among responders, of a constant HAQ for those remaining on bDMARDs and a worsening HAQ for those remaining on csDMARDs/BSC.

- **ERG comment**:

  Within the model this requires that either MTX or csDMARDs are used as placeholders for BSC rather than TCV_{IV} as in the main ERG report, with the ERG response to the company TC response providing scenario analyses that covered the company base case assumptions. The ERG will follow this approach for its revised base case. This assumes that those remaining on bDMARDs have a constant HAQ while those on csDMARDs and BSC have a worsening HAQ.

ACD Section 3.14: The modelled proportion of moderate RA patients progressing to severe RA appears low compared with UK ERAN data. This substantially reduces the robustness of the model estimates.

- **Company ACD response**:

  The company explores this in scenario analyses by doubling and tripling the HAQ coefficient estimated from SELECT trials data for mapping between the modelled HAQ progression and patients' DAS28.

- **ERG comment**:

  The ERG will explore the same scenario analyses.

ACD Section 3.15: The TA375 HAQ to pain mapping is preferred to that derived by the company from the SELECT trials.

- **Company ACD response**:

  The company suggests that Section 3.15 does not adequately reflect its concerns.

- **ERG comment**:

  None, other than to note that the ERG presented scenario analyses that applied the company HAQ to pain mapping that it derived from the SELECT trials and that these were fully considered by the AC.

  The ERG presents scenario analyses that apply the company HAQ to pain mapping function.

Much of the company response to the ACD assumes intensification to another active csDMARD, MTX in effect, is possible after upadacitinib. This company modelling does not seem to be of patients after failure of ≥ 2 csDMARDs who cannot intensify to another csDMARD. As per the original ERG report and section 1.7 of the ERG response to the company technical engagement submission, this fails to take into account the treatment sequence of intensifying to csDMARD before using upadacitinib. As in the main ERG report, the company model estimates that using upadacitinib before $csDMARD_s$ is not cost effective compared to using upadacitinib before $csDMARD_X$ before upadacitinib at conventional willingness to pay thresholds.

3. KEY ISSUES

3.1. Issue 1: Consistency between current assessment and TA375

As with the original company submission, Figure 1 fails to consider the mutually exclusive alternative treatment sequences. The obvious omission is the sequence of 1st line csDMARD followed by 2nd line advanced therapy followed by 3rd line BSC.

The ERG thinks that the company Figure 2 under Issue 1 unnecessarily includes csDMARDs with a 0% response rate subsequent to the 1st line treatments. This has relatively little effect upon results.

The company asserts that that the csDMARD-IR NMA placebo response rate should be the response rate assumed for csDMARDs for those who have failed an aDMARD. The ERG does not understand this argument. But it appears to relate to the company ACD response Table 6 figure of treatment sequences. This remains subject to the criticism that it omits the sequence of 1st line csDMARD followed by 2nd line advanced therapy followed by 3rd line BSC.

The company bDMARD-IR NMA provides response rate estimates for csDMARD: [redacted] moderate response and [redacted] good response compared to [redacted] moderate response and [redacted] good response in the csDMARD-IR NMA. Note that these are taken to apply to MTX, with the csDMARD-IR NMA providing estimates of [redacted] moderate response and [redacted] good response for intensified csDMARDs.

The company appears to think that the ACD requires a placebo effect of [redacted] moderate response and [redacted] good response, to be applied to 1st line placebo/BSC in the comparator arm against response rates for 1st line UPA+MTX of [redacted] moderate response and [redacted] good response.

The ERG reading of the ACD is that the AC viewed the company TC response approach of netting out the placebo effect favourably for estimating net patient benefits, hence 0% responses for 1st line placebo/BSC and net effects for 1st line UPA+MTX of [redacted] moderate response and [redacted] for good response. But the ACD also noted that this would probably underestimate net costs; i.e. the ICER would be biased and the true ICER would be higher than that estimated using this method.

The ERG agrees with the company that netting out placebo effects presents challenges.

3.2. Issue 2: Treatment sequences of different length

The issue is relatively simply put, as it is essentially the same issue as explored under Issue 1.

The active treatments in the NMAs have a placebo effect within them. As under Issue 1, if at some point in the treatment sequences an active treatment is compared with placebo/BSC and placebo/BSC is assumed to have a zero response rate, the longer treatment sequence will have the placebo effect applied more times than the shorter treatment sequence.

If it is sensible to equalise the number of times the placebo effect is applied in both arms, to make it a more like for like comparison, this can be achieved by either: assuming the placebo effect for placebo/BSC when it is alongside an active comparator; or, netting out the placebo effect from the active comparator; or, only comparing treatment sequences of equal lengths.

The company notes that the reapplication of the bDMARD-IR NMA estimates is likely to overestimate the treatment effect at later lines of treatment. The company scenario analyses that apply a 5% waning by line of treatment have little effect upon the ICER.

3.3. Issue 3: Inadequate explanation within the ACD

This issue is the same as Issue 2 above.

3.4. Issue 4: TA375 model validation work

This issue has not been explored in this document due to time constraints. The previous ERG commentary supplied in the ERG TC response was based upon estimates supplied by the company in its TC response.

3.5. Issue 5: Speed of transition to severe RA among non-responders

The company explores faster rates of transition to severe RA by doubling and tripling the HAQ to DAS28 coefficient it estimated from the SELECT trial data. The company reports the proportion in the comparator arm that worsens to severe RA under the tripling assumption, but not the proportion in the upadacitinib arm.

These are reasonable sensitivity analyses. But a full assessment of their reasonableness would require arm specific data on each SELECT trial's proportions of moderate RA patients who are non, moderate and good responders who worsened to severe RA by week 96.

The company modelling suggests that a faster transition to severe RA slightly worsens the cost effectiveness of UPA+MTX.

The ERG presents ICERs that apply the upadacitinib PAS, but use the list prices for all comparator treatments. NICE has directed that due to Humira being the only nationally available form of adalimumab, the ERG should assume all adalimumab use is Humira.

3.6. Issue 6: ACD description of Company net treatment effect approach

The ACD correctly describes the company method for netting out the placebo effect that the company applied in its TC response. The company approach of Table 7 appears to be a new methodology, and as per Figure 1 is subject to the criticisms outlined under Issue 1 above.

3.7. Issue 7: HAQ to pain mapping

The ERG thinks that the AC fully considered this issue. The ACD expresses a preference for the TA375 HAQ to pain mapping. The ERG supplies scenario analyses that apply the company mapping.

Note that table 9 is subject to the criticism outlined under Issue 1 above.

3.8. Issue 8: Omission of 2nd line MTX from treatment sequences

The company correctly notes that at position 2b, methotrexate tolerant, it modelled 2nd line MTX (csDMARD) after 1st line treatment failures in the UPA+MTX arm and the UPA monotherapy arm with this then followed by BSC, and compared these with 1st line MTX followed by 2nd line BSC.

The ACD summarises the company modelling at position 2a, methotrexate intolerant.

3.9. Issue 9: Upadacitinib monotherapy: Position 2a

This reiterates the company concerns.

4. COMPANY ACD RESPONSE: MODEL

4.1. Company ACD Response: Revisions to the model inputs

The ERG has cross checked the company revisions made to the Excel front end of the model.

1. The TA375 HAQ to pain score mapping cross checks with the original ERG revision.
2. The TA375 HAQ to IP cost mapping cross checks with the original ERG revision, with the exception of the ERG applying an inflationary uplift and the company not. The impact of this is minor.
3. The direct drug and administration cost revisions cross check with the ERG revisions for abatacept IV, golimumab and infliximab. There are some discrepancies with the rituximab costs. At list prices the company revises its drug and administration costs for the 6 month induction period and monthly thereafter of £3,461 and £385, compared to the ERG revised estimates of £2,201 and £367.
   - The original company model applied a 9 monthly drug cost of £3,143 but only one administration cost rather than the two required. This was then made pro-rata for the 6 month evaluation period by multiplying by 6/9. Given the subsequent monthly drug costs and administrations costs the ERG report was satisfied with the rituximab drug costings and only revised the administration costs. The revised company submission appears to apply the full £3,143 direct drug cost during the first six months, which can be argued as being more correct, but then appears to still apply a subsequent monthly direct drug and administration cost of £385.
   - The original company method underestimates the rituximab drug costs for the [redacted] of rituximab non-responders. The revised company method appears likely to overestimate the rituximab drug costs of the [redacted] of responders in months 7, 8 and 9.
   - Neither method may be correct. But there appears to be limited difference between the two. Given the focus upon moderate RA patients and rituximab only being used once patients progress to severe disease and fail on their first aDMARD for severe disease, the effect of this upon modelling results is likely to be limited.
   - The ERG retains the method applied when generating the ERG report, in part due to the stated company intention being to revise the model to be in line with the ERG revisions outlined in the final ERG report.

- For more details see the original ERG report section 5.3.2.2.
- The effect upon results of applying the original ERG revision compared to the company revision is small. It may be the main source of the relatively small discrepancies between the ERG modelling and the company modelling.

4. Clinical efficacy. For the company revised base case the NMA results for UPA+MTX and for MTX are applied. The company explored applying the NMA estimates for placebo. The company does not explore the SELECT trial head to head results, even when the comparison is of upadacitinib against placebo/BSC.
5. Within its response the company focusses UPA+MTX, but provides some analyses of UPA monotherapy for the methotrexate intolerant. For UPA monotherapy the ERG previously noted that the treatment effectiveness assumed for 1st line ADA among those progressing to severe RA was perversely assumed to be better for the bDMARD-IR NMA than for the csDMARD-IR NMA. The company has revised this assumption, with 1st line ADA response rate for the bDMARD-IR NMA now being 95% those of the csDMARD-IR NMA. The ERG thinks this is more reasonable.
6. Within the company model, ETN+MTX is used as a placeholder for ADA+MTX so that the clinical effectiveness estimates for ADA+MTX from the csDMARD-IR NMA can be applied for the comparator arm while the clinical effectiveness estimates for ADA+MTX from the bDMARD-IR NMA can be applied for the upadacitinib arm. Within this there appears to be a minor error in the drug and administration costs that are applied for ETN+MTX with these not being equal to the corresponding ADA+MTX costs[1]. This has minimal effect upon results.

4.2. Company ACD response results

In its 18 March 2020 response to the company ACD response the ERG supplied cross check results for the analyses submitted by the company in the 3rd column using the ERG amended 03 March 2020 company model, ERG 1. The ERG further cross checked these results in the ERG amended 29 Aug 2019 company model in the 4th column, ERG 2. But these results included the adalimumab PAS. The ERG provided its own set of analyses that attempted to replicate the company results, but excluding the adalimumab PAS.

The company has subsequently provided an updated set of results that exclude the adalimumab PAS. As a consequence, the ERG initial cross checks and results excluding the

[1] Corrected in the 28022020 model version by setting Drug Costs AC41:AE42 to be equal to AC23:AE24

adalimumab PAS are now redundant. The reader is referred to the company submission for its ACD response results, with the ERG only providing a brief commentary on these below.

4.3. Company ACD response: Table 4

These analyses are subject to the same criticism as the original company modelling. The mutually exclusive alternatives are not considered: The sequence of csDMARD followed by UPA+MTX is excluded from the analysis. Previous ERG work has shown that UPA+MTX followed by csDMARD has an extremely poor cost effectiveness compared to csDMARD followed by UPA+MTX. As intuition suggests, it is more cost effective to try the much less expensive csDMARD first to see if a response can be achieved, and only if a response is not achieved to then try the much more expensive upadacitinib.

As in the original ERG report, it appears that the company model estimates that 1st line upadacitinib is not cost effective at position 1.

4.4. Company ACD response: Table 6

This is subject to the same criticism as Table 4 in that it does not consider 2nd line use of UPA+MTX. Intuition suggests that it is more cost effective to try the much less expensive csDMARD first to see if a response can be achieved, and only if a response is not achieved to then try the much more expensive upadacitinib.

4.5. Company ACD response: Table 7

It is unclear why the company does not present results for the same range of scenarios as in CS Table 4. This is subject to the same criticism as Table 4 in that it does not consider 2nd line use of UPA+MTX. Intuition suggests that it is more cost effective to try the much less expensive csDMARD first to see if a response can be achieved, and only if a response is not achieved to then try the much more expensive upadacitinib.

4.6. Company ACD response: Table 8

It is unclear why the company does not present results for the same range of scenarios as in CS Table 4.

4.7. Company ACD response: Tables 9 and 10

It is unclear why the company does not present results for the same range of scenarios as in CS Table 4.

Table 9 is subject to the same criticism as Table 4 in that it does not consider 2nd line use of UPA+MTX. Intuition suggests that it is more cost effective to try the much less expensive csDMARD first to see if a response can be achieved, and only if a response is not achieved to then try the much more expensive upadacitinib.

The main ERG report provided scenario analyses that apply the HAQ to pain mapping function that the company estimates from SELECT data. This document will also provide these for the additional ERG modelling.

4.8. Company ACD response: Table 11 and Table 12

It is unclear why the company does not present results for the same range of scenarios as in CS Table 4.

5. COMMENTS FROM PATIENT REPRESENTATIVE AT AC

The ERG report raised the concern that some moderate RA patients not achieving a moderate EULAR response to upadacitinib might remain on upadacitinib treatment.

If upadacitinib is approved for moderate RA at position 2, it seems likely that those without a moderate EULAR response but with a better response than that of their previous csDMARDs would want to remain on upadacitinib treatment.

The patient representative was clear that if she was a moderate RA patient receiving upadacitinib after having exhausted csDMARD combinations she would be unwilling to have upadacitinib treatment withdrawn and would vigorously fight this. It was unclear, however, whether patients in this position would vigorously resist withdrawal of upadacitinib if response was less than a moderate EULAR response but better than response to previous csDMARDs.

In this context it can be noted that a significant component of the DAS28 is the general health status, as reported by the patient on a visual analogue scale of 100mm. Within the DAS28 the coefficient on the general health variable is 0.014 per mm. For moderate RA patients, a moderate EULAR response requires a DAS28 improvement of at least 0.6. This raises the prospect of patients who have had some benefit from upadacitinib over-reporting the general health gains from receiving upadacitinib in order to 'manufacture' a moderate EULAR response. This may be preferable to fighting withdrawal of upadacitinib due to inadequate response.

It should also be borne in mind that this consideration raises the possibility of patients reporting very bad general health in order to qualify for treatment with the aDMARDs. The extent that this is possible but has not occurred argues against the concern that moderate EULAR responses could or would be artificially generated.

The above concerns may mean that some moderate RA patients without a moderate EULAR response would continue upadacitinib treatment. This would worsen the cost effectiveness of upadacitinib for moderate RA.

6. NMA RESULTS VERSUS TRIAL HEAD TO HEAD RESULTS

For both the severe RA modelling and the moderate RA modelling the revised ERG base case applied the company NMA estimates. This is appropriate for the severe RA modelling as this enables a comparison with the relevant active comparator. But for the moderate RA modelling where upadacitinib was being compared with placebo or best supportive care it can be argued that the appropriate source of evidence is not the NMA but the direct head to head results of the SELECT placebo controlled trials.

The NICE methods guide states: "*Data from head-to-head RCTs should be presented in the reference-case analysis. When technologies are being compared that have not been evaluated within a single RCT, data from a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis if appropriate*."

It can be noted that there was some lack of clarity about how the placebo effect of the NMA was estimated. Applying the head to head trial results is complicated by there being no pooled estimate. But it can be noted that the net effect of upadacitinib over placebo estimated in the csDMARD-IR NMA is typically somewhat larger than the net effect of upadacitinib over placebo observed during the SELECT trials.

Table 1. EULAR response rates: NMA vs SELECT csDMARD-IR trials vs model

			EULAR response rates					
			Control		UPA+MTX		Net	
SELECT	**Wk**	**Cont**	**Mod.**	**Good**	**Mod.**	**Good**	**Mod.**	**Good**
For comparison with UPA+csDMARDs modelling								
csDMARD-IR NMA	..	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COMPARE EULAR NRI	26	PBO	24%	17%	19%	54%	-5%	37%
COMPARE EULAR LOCF	26	PBO	36%	18%	31%	59%	-5%	41%
COMPARE (ACR mapped)	12	PBO	24%	22%	31%	40%	7%	18%
COMPARE (ACR mapped)	26	PBO	23%	23%	30%	40%	7%	17%
NEXT (ACR mapped)	12	PBO	24%	22%	31%	36%	6%	14%
Modelling UPA+csDMARD	..	BSC	0%	0%	[redacted]	[redacted]	[redacted]	[redacted]

Under Issue 1 the company states that the ERG preferred source for placebo response rates is the company NMA. This exaggerates any ERG preference and ignores the importance of the head-to-head RCT results.

The ERG provided sensitivity analyses which applied the head to head results of the SELECT trials.

7. ERG MODELLING IN THE LIGHT OF THE ACD AND COMPANY ACD RESPONSE

The modelling results which follow use the ERG amended 29 Aug 2019 model. The results below include the upadacitinib PAS, apply the list price of Humira for adalimumab and apply the list prices of the other treatments.

For the main ERG analyses where upadacitinib is presented alongside placebo/BSC the ERG presents two sets of estimates: one that retains the placebo effect for both upadacitinib and placebo/BSC; and, one which nets it out from both upadacitinib and placebo/BSC causing placebo/BSC to have zero response rates.

For its revised base cases the ERG assumes that those on bDMARDs have no HAQ worsening, while those on csDMARDs and BSC have a worsening HAQ.

Given the company ACD response the ERG considers positions for moderate RA patients who have has an inadequate response to ≥ 2csDMARDs: Position 2a: MTX intolerant, RTX tolerant; and, Position 2b: MTX tolerant, RTX tolerant.

Due to time constraints the ERG has not been able to consider Position 2c: MTX intolerant, RTX intolerant. The ERG draws attention to the similarity of the ICERs for Position 2a and Position 2c.

The ERG previously noted that for position 2a results were to a degree perverse due ADA monotherapy being assumed to have a higher response rate for bDMARD-IR than for csDMARD-IR. The company has addressed this by applying a 95% waning for the bDMARD-IR response rates. The ERG follows this approach.

Where appropriate the ERG provides the scenario analyses of its previous reports.

1. SA01: Clinical effect estimates (base case company NMA)
    a) SELECT-COMPARE EULAR response rates NRI estimates
    b) SELECT-COMPARE EULAR response rates LOCF estimates
    c) SELECT-COMPARE EULAR response rates ACR mapped
    d) SELECT-NEXT EULAR response rates ACR mapped

e) SELECT-MONOTHERAPY EULAR response rates ACR mapped[2]

2. SA02: Treatment sequences for severe RA

   a) Scenario 01: Subcutaneous abatacept being used instead of sarilumab in the upadacitinib sequence3.

   b) Scenario 02: Upadacitinib being used instead of sarilumab in the comparator treatment sequence.

   c) Scenario 03: Scenarios 01 and 02 combined.

3. SA03: Company SELECT HAQ to Pain mapping function

4. SA04: Wane the treatment effect by treatment line by 5%.

5. SA05: Speed the transition to severe RA by doubling and tripling the HAQ to DAS28 coefficient that the company estimated from SELECT data.

For SA01e, SELECT-MONOTHERAPY was unusual in having an active comparator of MTX. As a consequence, SA01e may be better seen as the cost effectiveness of upadacitinib monotherapy compared to methotrexate. Within this comparison, it is not obvious that netting out the comparator arm treatment effect is valid, and the placebo effect is unknown.

For SA02, particularly for position 2a which involves more assumptions about clinical effectiveness estimates, the ERG sees these primarily as cost scenarios and suggests that the changes in the net QALYs and ICERs are not the focus.

The ERG has had repeated problems running the company model. It may at times not pick up all the changes in the Excel front end prior to running the VBA simulation. Or there may be other reasons for the apparent instability the ERG has experienced. The ERG has tried to be careful and has typically run the model at least twice for the analyses that follow. But errors remain a possibility. The ERG urges the company to cross check both the ERG revisions to the AiC version of the 29 Aug 2019 model and the following results. The ERG is happy to answer any company questions about the ERG revisions to the AiC version of the 29 Aug 2019 model.

[2] The use of SELECT-MONOTHERAPY for modelling monotherapy upadacitinib can be criticised due to SELECT-MONOTHERAPY having an active control of MTX when modelling a comparator of placebo / BSC.

[3] For abatacept monotherapy the bDMARD-IR clinical effectiveness is assumed by the ERG to be 95% that of the company assumed cDMARD-IR effectiveness.

Table 2. ERG analyses: Pos 2a: UPA vs PBO / BSC: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

	Absolute effect estimates			Effect estimates minus placebo		
	∆Cost	∆QALY	ICER	∆Cost	∆QALY	ICER
Base case sequences	[redacted]	[redacted]	£32,432	[redacted]	[redacted]	£18,295
SA01a: COMPARE EULAR NRI		[redacted]			[redacted]	
SA01b: COMPARE EULAR LOCF		[redacted]			[redacted]	
SA01c: COMPARE EULAR ACR mapped		[redacted]			[redacted]	
SA01d: NEXT EULAR ACR mapped		[redacted]			[redacted]	
SA01e: MONOTHERAPY EULAR ACR mapped	[redacted]	[redacted]	£50,119	[redacted]	[redacted]	..
SA02a: Sev. RA ABT_{SC} use after mod. RA UPA use	[redacted]	[redacted]	£34,312	[redacted]	[redacted]	£21,998
SA02b: Sev. RA UPA use if no mod. RA UPA use	[redacted]	[redacted]	£40,812	[redacted]	[redacted]	£29,736
SA02c: SA2a + SA2b	[redacted]	[redacted]	£42,507	[redacted]	[redacted]	£35,070
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£27,813	[redacted]	[redacted]	£15,327
SA04: 5% treatment waning	[redacted]	[redacted]	£31,839	[redacted]	[redacted]	£18,962
SA04: Double HAQ to DAS28 coefficient	[redacted]	[redacted]	£24,825	[redacted]	[redacted]	£8,547
SA05: Triple HAQ to DAS28 coefficient	[redacted]	[redacted]	£22,369	[redacted]	[redacted]	£1,270

Abbreviations: ABT, abatacept; ACR, Americal College of Rheumatology; BSC, best supportive care; csDMARD, conventional synthetic disease modifying antirheumatic drug; DAS, disease activity score; ERG, Evidence Review Group; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaite; ICER, incremental cost-effectiveness ratio; LOCF, last observation carried forward; MTX, methotrexate; NRI, non-responder imputation; PBO, placebo; QALY, quality adjusted life year; RA, rheumatoid arthritis; RTX, rituximab; Sev, severe; UPA, upadacitinib; vs, versus

Table 3. ERG analyses: Pos 2b: UPA + MTX vs PBO / BSC: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

	Absolute effect estimates			Effect estimates minus placebo		
	∆Cost	∆QALY	ICER	∆Cost	∆QALY	ICER
Base case sequences	[redacted]	[redacted]	£28,356	[redacted]	[redacted]	£15,881
SA01a: COMPARE EULAR NRI	[redacted]	[redacted]	£31,484	[redacted]	[redacted]	*
SA01b: COMPARE EULAR LOCF	[redacted]	[redacted]	£31,991	[redacted]	[redacted]	*
SA01c: COMPARE EULAR ACR mapped	[redacted]	[redacted]	£40,780	[redacted]	[redacted]	£17,974
SA01d: NEXT EULAR ACR mapped	[redacted]	[redacted]	£48,390	[redacted]	[redacted]	£19,052
SA01e: MONOTHERAPY EULAR ACR mapped	[redacted]	[redacted]	..	[redacted]	[redacted]	..
SA02a: Sev. RA ABT_{SC} use after mod. RA UPA use	[redacted]	[redacted]	£31,247	[redacted]	[redacted]	£21,229
SA02b: Sev. RA UPA use if no mod. RA UPA use	[redacted]	[redacted]	£35,385	[redacted]	[redacted]	£25,946
SA02c: SA2a + SA2b	[redacted]	[redacted]	£38,166	[redacted]	[redacted]	£31,341
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£24,420	[redacted]	[redacted]	£13,518
SA04: 5% treatment waning	[redacted]	[redacted]	£29,596	[redacted]	[redacted]	£17,554
SA04: Double HAQ to DAS28 coefficient	[redacted]	[redacted]	£22,734	[redacted]	[redacted]	£5,874
SA05: Triple HAQ to DAS28 coefficient	[redacted]	[redacted]	£17,893	[redacted]	[redacted]	Dominant

Abbreviations: ABT, abatacept; ACR, Americal College of Rheumatology; BSC, best supportive care; csDMARD, conventional synthetic disease modifying antirheumatic drug; DAS, disease activity score; ERG, Evidence Review Group; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaite; ICER, incremental cost-effectiveness ratio; LOCF, last observation carried forward; MTX, methotrexate; NRI, non-responder imputation; PBO, placebo; QALY, quality adjusted life year; RA, rheumatoid arthritis; RTX, rituximab; Sev, severe; UPA, upadacitinib; vs, versus

Notes:

* Not amenable to simple netting out due to higher moderate response for PBO / BSC than for UPA + MTX

Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]

ICERs prior to AC2

17/08/2020

1 ICERs requested by NICE prior to AC2

Based upon the ERG's response to the second error check documents (document dated 06-05-2020).

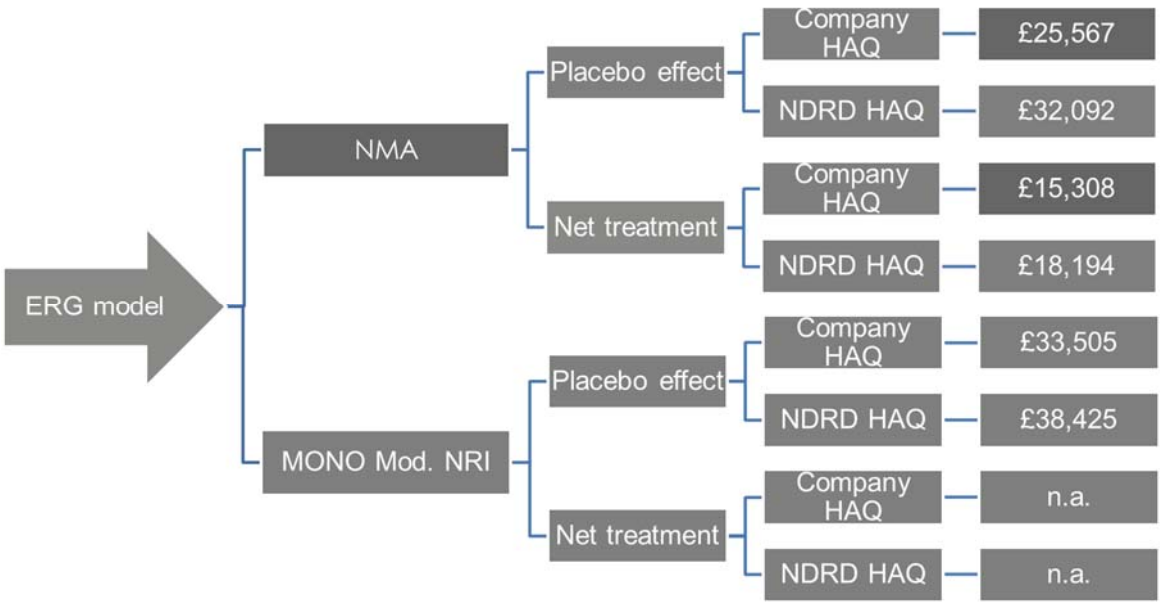
Note that for all analyses the combination of SELECT trial EULAR and company HAQ are new so have not been seen by the company and have not been error checked.

Also, some net treatment effects are not estimable due to the simple subtraction of moderate and good response rates resulting in at least one negative value.

Figure 1 through to **Error! Reference source not found.** are based upon variations around the ERG base case:

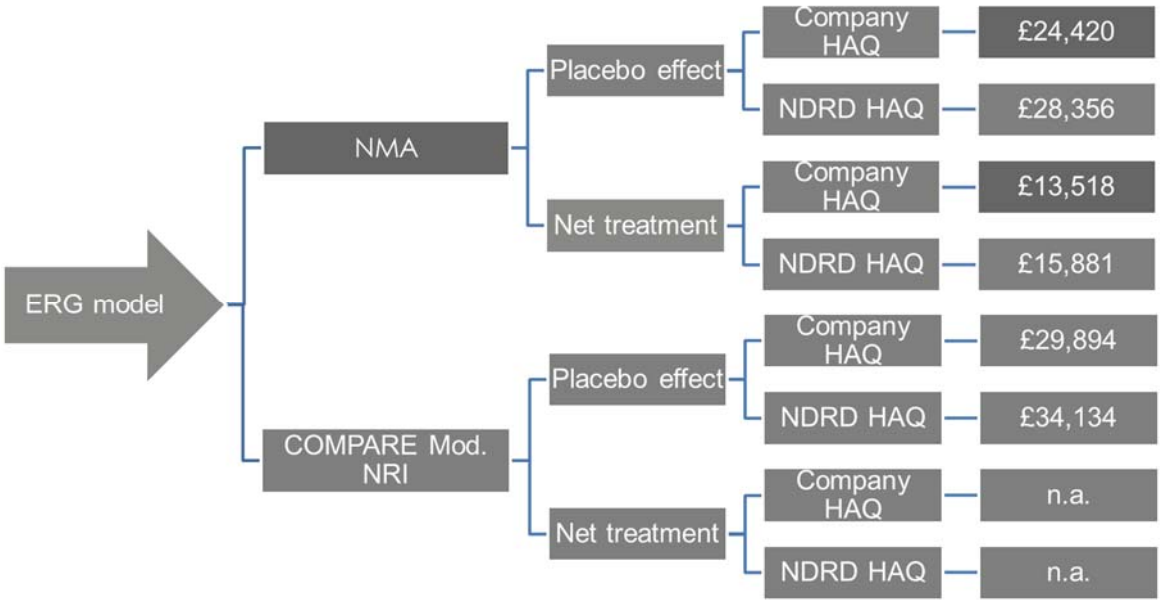
- Placebo effect vs net treatment effect
- TA375 HAQ to pain mapping vs company SELECT trial HAQ to pain mapping
- Company NMA results vs SELECT trials' head to head results

Figure 1. Position 2a UPA PAS other drugs at list prices. SELECT – MONOTHERAPY – EULAR NRI moderate RA



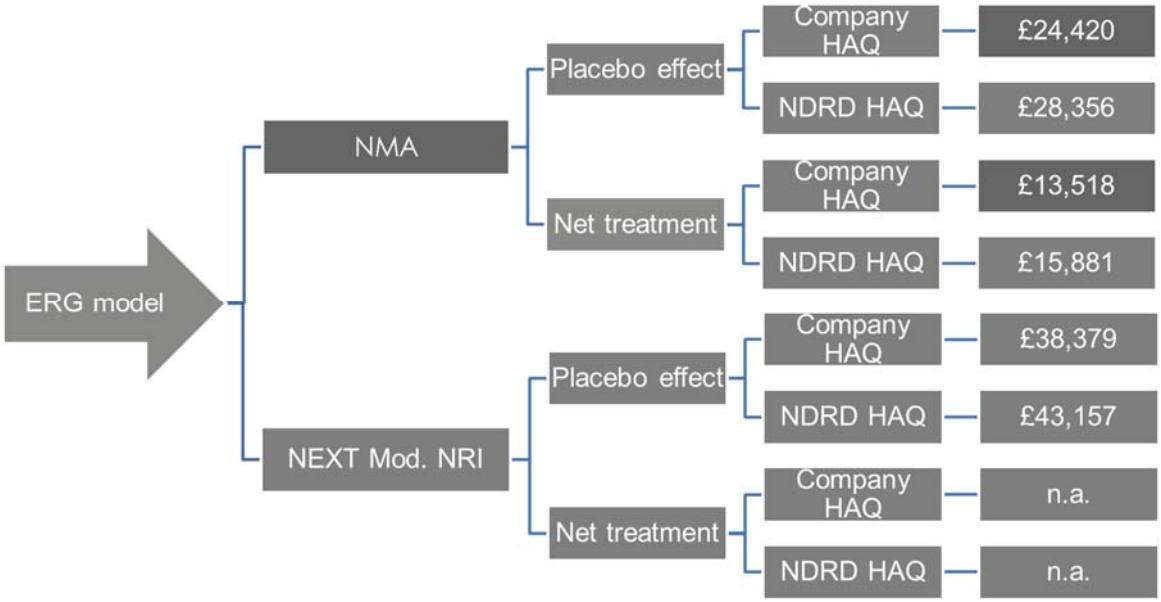
Abbreviations: ERG, Evidence Review Group; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; Mod, moderate; n.a., not available; NDRD, National Databank for Rheumatic Diseases; NMA, network meta-analysis; NRI, non-responder imputation; PAS, patient access scheme; RA, rheumatoid arthritis; UPA, upadacitinib

Figure 2: Position 2b: UPA PAS other drugs at list prices. SELECT – COMPARE – EULAR NRI moderate RA



Abbreviations: ERG, Evidence Review Group; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; Mod, moderate; n.a., not available; NDRD, National Databank for Rheumatic Diseases; NMA, network meta-analysis; NRI, non-responder imputation; PAS, patient access scheme; RA, rheumatoid arthritis; UPA, upadacitinib

Figure 3: Position 2b: UPA PAS other drugs at list prices. SELECT – NEXT – EULAR NRI moderate RA

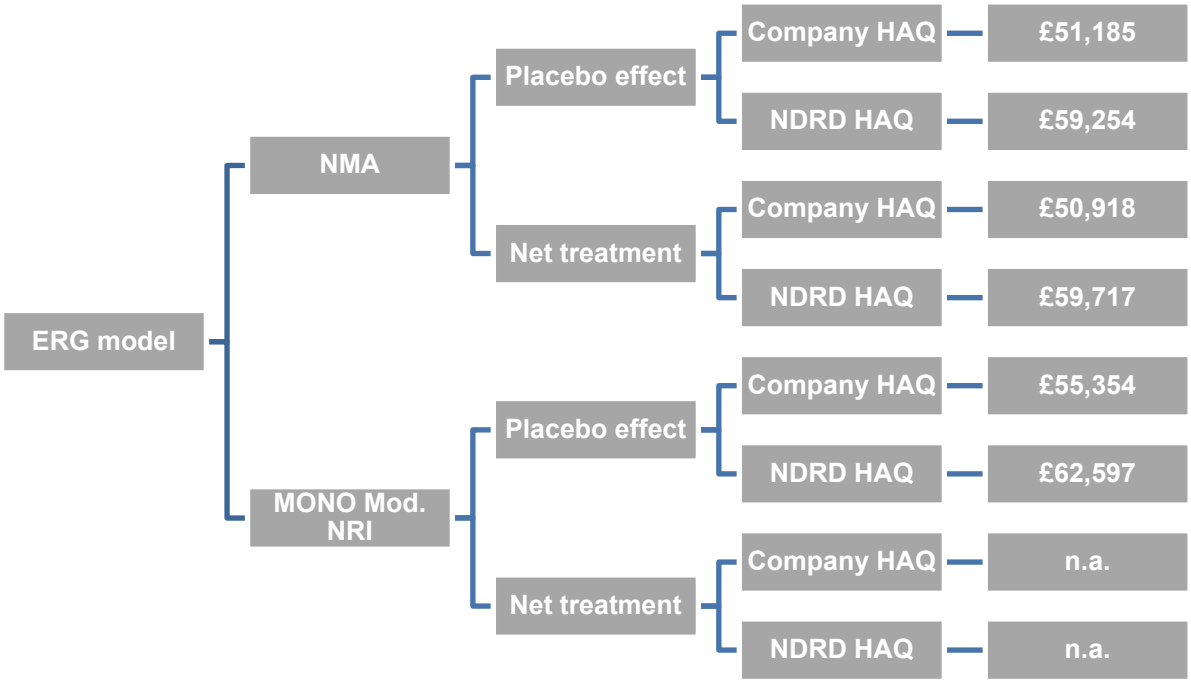


Abbreviations: ERG, Evidence Review Group; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; Mod, moderate; n.a., not available; NDRD, National Databank for Rheumatic Diseases; NMA, network meta-analysis; NRI, non-responder imputation; PAS, patient access scheme; RA, rheumatoid arthritis; UPA, upadacitinib

Figure 4 through to 6 provide a similar set of scenario analyses as the previous figures, but are based upon:

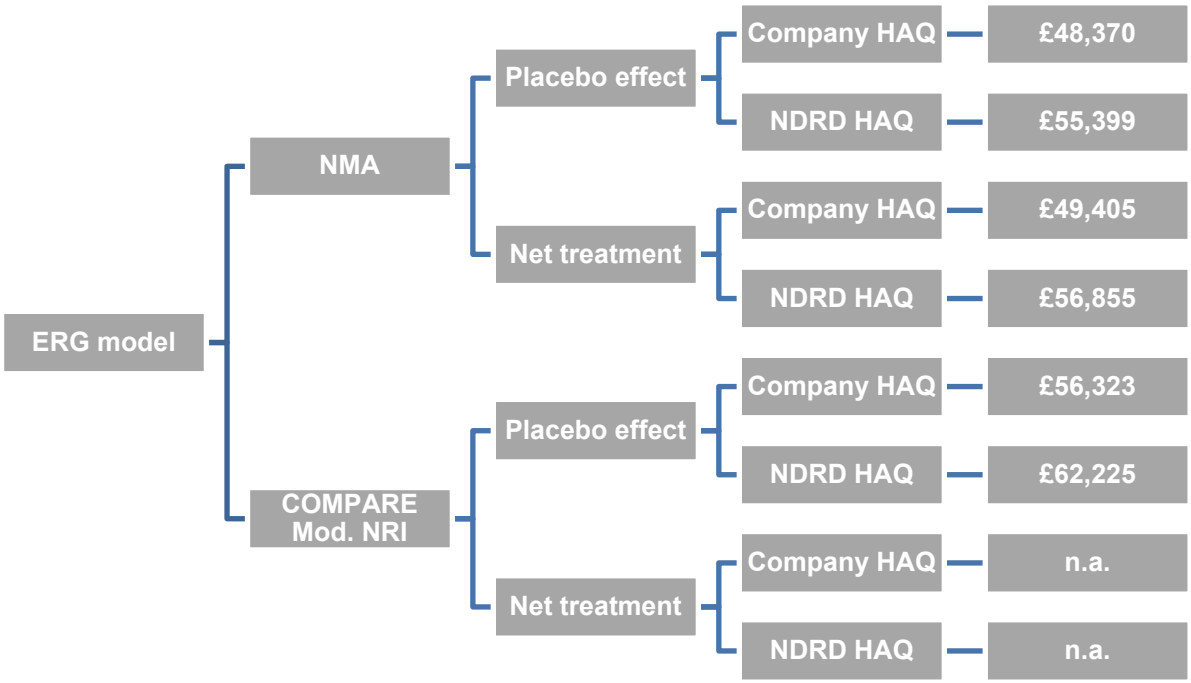
- Severe RA patients previously treated with upadacitinib when in moderate RA will be treated with subcutaneous abatacept rather than sarilumab.
- Severe RA patients not previously treated with upadacitinib when in moderate RA will be treated with upadacitinib rather than sarilumab.
- Tripling the HAQ to DAS28 coefficient.

Figure 4. Position 2a UPA PAS other drugs at list prices. SELECT – MONOTHERAPY – EULAR NRI moderate RA



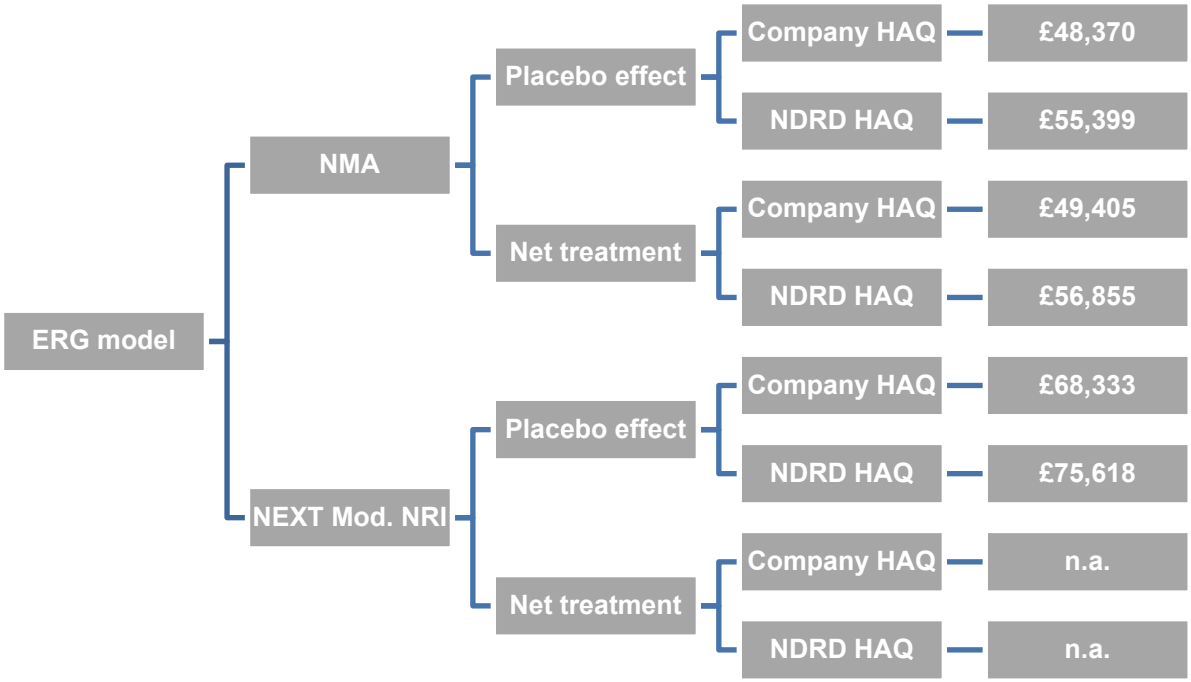
Abbreviations: ERG, Evidence Review Group; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; Mod, moderate; n.a., not available; NDRD, National Databank for Rheumatic Diseases; NMA, network meta-analysis; NRI, non-responder imputation; PAS, patient access scheme; RA, rheumatoid arthritis; UPA, upadacitinib

Figure 5: Position 2b: UPA PAS other drugs at list prices. SELECT – COMPARE – EULAR NRI moderate RA



Abbreviations: ERG, Evidence Review Group; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; Mod, moderate; n.a., not available; NDRD, National Databank for Rheumatic Diseases; NMA, network meta-analysis; NRI, non-responder imputation; PAS, patient access scheme; RA, rheumatoid arthritis; UPA, upadacitinib

Figure 6: Position 2b: UPA PAS other drugs at list prices. SELECT – NEXT – EULAR NRI moderate RA



Abbreviations: ERG, Evidence Review Group; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; Mod, moderate; n.a., not available; NDRD, National Databank for Rheumatic Diseases; NMA, network meta-analysis; NRI, non-responder imputation; PAS, patient access scheme; RA, rheumatoid arthritis; UPA, upadacitinib

Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]

ERG additional analyses after AC2

15/09/2020

Subsequent to AC2 NICE asked the ERG to estimate the cost effectiveness of upadacitinib for moderate RA patients who have failed to respond to or have lost response to csDMARDs: position 2b for the methotrexate tolerant, the larger patient group, and position 2a for the methotrexate intolerant. These analyses apply the SELECT trials' head-to-head moderate RA patients' EULAR response rates and triple the company HAQ to DAS28 coefficient to increase the rate at which non-responders transition to severe RA. They also assume that among those transitioning to severe RA in the upadacitinib arm subcutaneous abatacept will be used at 3rd line.

Three alternative assumptions are explored:

- Applying (a) the TA375 NDRD HAQ to pain mapping and (b) the company SELECT trials HAQ to pain mapping.
- Assuming that among those transitioning to severe RA in the comparator arm (a) upadacitinib will be used at 3rd line and (b) sarilumab will be used at 3rd line.
- [redacted]

[redacted]

Table 1. Annual cost per patient of upadacitinib at the various PASs

PAS	Annual cost per patient
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

An issue arises about point 2 above. The ERG modelling that applied the company NMA estimates applied the csDMARD-IR NMA estimates for upadacitinib when used for moderate RA patients and the bDMARD-IR NMA estimates for upadacitinib when used for severe RA

patients. The ERG modelling that applied the SELECT trial head-to-head estimates[1] applied the SELECT trial moderate patients' EULAR estimates for upadacitinib when used for moderate RA patients but retained the bDMARD-IR NMA estimates for upadacitinib when used for severe RA patients. The ERG thinks this remains the most reasonable approach given that the EULAR estimates for 3rd line subcutaneous abatacept were also drawn from the bDMARD-IR NMA.

It could be argued that the SELECT trial severe patients' EULAR estimates should be applied for 3rd line upadacitinib use. This would worsen the cost effectiveness estimate for upadacitinib use at position 2b, due to the bDMARD-NMA total EULAR response estimates for upadacitinib being lower than that of the SELECT trials severe patients, and also having a lower proportion of good responders than among the SELECT trials severe patients. But the ERG thinks that it is unreasonable to have different sources of efficacy for treatments at the same point in the treatment sequence.

It should also be remembered that for the following treatment sequences for moderate RA:

- MTX->UPA->csDMARDs: upadacitinib at position 1
- MTX->csDMARDs->UPA: upadacitinib at position 2

It was found that the cost effectiveness of using upadacitinib at position 1 was extremely poor when compared to using upadacitinib at position 2. As a consequence, upadacitinib at position 1 was deemed not cost effective.

The ERG thinks that it is sensible to consider the placement of upadacitinib within the treatment sequence. So it is sensible to compare sequences using upadacitinib at position 2 with sequences using upadacitinib at 3rd line for severe RA. If this is not valid, it may be similarly invalid to compare sequences using upadacitinib at position 1 with sequences using upadacitinib at position 2. This could complicate the consideration of upadacitinib use among patients with moderate RA and might call into question the AC preference for position 2.

With regards point 3 above the company has revised its PAS twice during the course of the assessment. The first increase from [redacted] to [redacted] applied to both moderate RA and severe RA. The second increase from [redacted] to [redacted] apparently applies only to severe RA, because the company states that it will withdraw this offer if the AC does not approve upadacitinib for

[1] Note that the SELECT trial head-to-head results are applied at moderate RA with the SELECT trial upadacitinib EULAR response rates being applied in the upadacitinib arm and the SELECT trial placebo EULAR response rates being applied in the comparator arm.

moderate RA. The ERG does not know whether PASLU has formally approved the [redacted] PAS, and if it has whether the company can withdraw the [redacted] PAS and revert to the [redacted] PAS.

The ERG analyses presented at AC2 that applied the [redacted] upadacitinib PAS applied it to both moderate RA and severe RA. All analyses in this document apply the highest PAS when using upadacitinib for moderate RA, including the scenarios that increase it to [redacted] and [redacted] but retain the [redacted] PAS when using upadacitinib for severe RA; i.e. the upadacitinib arm has the highest PAS applied but the comparator arm retains the [redacted] PAS. If the company cannot withdraw its PAS subsequent to PASLU approval, applying the [redacted] PAS in the comparator arm is incorrect.

The ERG has had to further revise the company model to differentiate the upadacitinib PAS by arm. This has led to minor discrepancies between the results reported for AC2 and the current model; e.g. for position 2b and an upadacitinib PAS of [redacted] in both arms applying the next NRI moderate EULAR response rates the ICERs were previously [redacted] when using the NRDR pain mapping and [redacted] when using the company pain mapping, whereas the current model suggests [redacted] and [redacted] respectively. The effect of applying a [redacted] upadacitinib PAS in the upadacitinib arm and a [redacted] upadacitinib PAS in the comparator arm for the NDRD pain mapping scenario is shown below.

Table 2. Effects of differentiating upadacitinib PAS by arm

[redacted]	UPA+MTX	Comp.	Net
Costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	0.382
ICER			[redacted]
[redacted]	UPA+MTX	Comp.	Net
Costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	0.382
ICER			[redacted]
[redacted]	UPA+MTX	Comp.	Net
Costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	0.382
ICER			[redacted]

The effects of retaining the [redacted] PAS in the comparator arm are relatively muted compared to the scenario which applied the [redacted] PAS in both arms.

For the upadacitinib PASs that are explored, the net annual costs per patient compared to adalimumab costed as Humira, as the May 2019 average and as Imraldi are shown in Table 3. Note that in May 2019 the biosimilars accounted for 64% of the market and Humira the remainder. The biosimilar market share was increasing rapidly, with the exception of the S. London region which was restricted to use of Humira and the more expensive Hulio, so remained 100% Humira.

Table 3. Upadacitinib PASs and net annual cost per patient relative to adalimumab

		Upadacitinib PAS			
		[redacted]	[redacted]	[redacted]	[redacted]
	Annual cost	[redacted]	[redacted]	[redacted]	[redacted]
Humira	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
May 2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imraldi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All the following analyses apply the [redacted] upadacitinib PAS in the comparator arm and the comparator PASs, these affecting the costs of treating severe RA.

Table 4. Cost effectiveness estimates: £ per QALY

			Severe RA: 3rd line		Upadacitinib PAS		
Pos	Trial	Pain	UPA arm	Comp.arm	[redacted]	[redacted]	[redacted]
2b	NEXT	NDRD	ABT+MTX	UPA+MTX	[redacted]	[redacted]	[redacted]
2b	NEXT	Comp.	ABT+MTX	UPA+MTX	[redacted]	[redacted]	[redacted]
2b	NEXT	NDRD	ABT+MTX	SRL+MTX	[redacted]	[redacted]	[redacted]
2b	NEXT	Comp.	ABT+MTX	SRL+MTX	[redacted]	[redacted]	[redacted]
2b	COMPARE	NDRD	ABT+MTX	UPA+MTX	[redacted]	[redacted]	[redacted]
2b	COMPARE	Comp.	ABT+MTX	UPA+MTX	[redacted]	[redacted]	[redacted]
2b	COMPARE	NDRD	ABT+MTX	SRL+MTX	[redacted]	[redacted]	[redacted]
2b	COMPARE	Comp.	ABT+MTX	SRL+MTX	[redacted]	[redacted]	[redacted]
2a	MONO	NDRD	ABT	UPA	[redacted]	[redacted]	[redacted]
2a	MONO	Comp.	ABT	UPA	[redacted]	[redacted]	[redacted]
2a	MONO	NDRD	ABT	SRL	[redacted]	[redacted]	[redacted]
2a	MONO	Comp.	ABT	SRL	[redacted]	[redacted]	[redacted]

For position 2b the ERG thinks that SELECT-NEXT is the trial of interest due to it being conducted among patients who had an inadequate response to csDMARDs (at least one of

MTX, sulfasalazine or leflunomide), whereas SELECT-COMPARE focused on patients who had an inadequate response to MTX with or without trial of other csDMARDs. The proportions in each trial with exposure to 1, 2, 3 and 4 or more prior synthetic DMARDs is as per Table 5. Note that this is taken from the relevant CSR for the final analysis set, and so is not restricted to the moderate RA subgroup. It show that [redacted] of SELECT-COMPARE patients, [redacted] had only had prior synthetic DMARD, whereas in SELECT-NEXT [redacted] of patients had had only one prior synthetic DMARD.

Table 5. Patient distributions by number of prior synthetic DMARDs

	COMPARE			NEXT		
Priors	PBO	UPA 15mg	Pooled	PBO arm	UPA arm	Pooled
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]