Response to:

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Abatacept, adalimumab, etanercept, infliximab and rituximab for the treatment of rheumatoid arthritis after the failure of a TNF-α inhibitor

Prepared by:

Bristol-Myers Squibb Pharmaceuticals Limited

24th March 2010

CONFIDENTIAL VERSION

Response to the Appraisal Consultation Document: abatacept, adalimumab, etanercept, infliximab and rituximab for the treatment of rheumatoid arthritis after the failure of a TNF-α inhibitor

Confidential information is highlighted and underlined, e.g. Orencia

Approved Name of Medicinal Product:	abatacept
Brand Name:	Orencia
Company:	Bristol-Myers Squibb Pharmaceuticals Ltd
Submitted by:	[redacted]
Position:	[redacted] Economics and Outcomes Research
Date:	24th March 2010

Bristol-Myers Squibb (BMS) welcomes the opportunity to review and comment on the Appraisal Consultation Document (ACD) relating to the ongoing appraisal of abatacept, adalimumab, etanercept, infliximab and rituximab for the treatment of rheumatoid arthritis (RA) after the failure of a TNF-α inhibitor (anti-TNF).

BMS disagrees with the preliminary recommendation of the ACD not to recommend abatacept.

We have significant concerns that the Appraisal Committee (AC) has been misled by a flawed analysis by the Assessment Group (AG). Please find a summary of our concerns below:

1. The Birmingham Rheumatoid Arthritis Model (BRAM) uses rituximab as a comparator for abatacept and the anti-TNFs. Rituximab is an inaccurate and inappropriate comparator in the BRAM because patients with rheumatoid factor (RF) negative RA are less likely to respond to rituximab.

The AG justifies the use of rituximab as a comparator with the argument that they were not able to identify differences in the effectiveness of rituximab in patients with RF negative or positive RA. The ACD acknowledges (section 4.1.12) that in the REFLEX trial, absolute response rates were lower in both the rituximab and the placebo groups for people who were RF negative compared with those who were RF positive. It further acknowledges that when

participants were stratified according to both RF and anti-cyclic citrullinated peptide antibody (anti-CCP) status, data suggest a greater treatment response in people who were RF positive than in those who were RF negative. However, the AG noted that this retrospective analysis should be treated with caution.

BMS believes that these data highlight that rituximab is not an optimal treatment option for patients who have RF negative RA.

The BMS position is further supported by the findings of the trials studying rituximab for the treatment of RA after the failure of conventional disease modifying anti-rheumatic drugs (DMARDs) (i.e. MIRROR, SERENE) (1). In a combined analysis of these studies, RF positive patients were 2–3 times more likely to achieve ACR (American College of Rheumatology) responses compared with patients negative for both autoantibodies (1). This is further supported by clinical opinion (2).

BMS acknowledges that the available data from randomised clinical trials (RCTs) for rituximab in anti-TNF failure patients may not be sufficient to be used in the BRAM, but asks the AC to acknowledge the large degree of uncertainty regarding the effectiveness of rituximab for these patients.

In addition, recent data from the United Kingdom (UK) suggests, that B-cell depletion with rituximab is linked with the development of psoriasis (3). As a consequence, the use of rituximab for some patients may also harm.

Therefore, BMS asks the AC to accept that rituximab should not be used as a comparator in the BRAM. Instead conventional DMARDs should be used as the appropriate comparator.

2. The BRAM (in the reference case) assumes no Health Assessment Questionnaire (HAQ) score deterioration whilst on treatment for all biologic DMARDs irrespective of their mechanism of action. However, rituximab is associated with radiographic deterioration whilst on treatment, which is not what is observed with abatacept or the anti-TNFs. In one scenario analysis the AG incorrectly assumes a worsening of the HAQ score whilst being treated with abatacept although this scenario is not supported by the available evidence.

Therefore BMS asks the AG to use a worsening of the HAQ score in the BRAM whilst on treatment with rituximab, but not for abatacept.

3. The BRAM insists on using a treatment interval of 8.7 months for rituximab based on historical data. In the current clinical environment in the UK this is too long for rituximab. Recent market research showed an average re-treatment interval with rituximab of 5.9 months (4). This is supported by clinical opinion (2), which states that although longer treatment intervals were common historically, physicians now use shorter 6 month re-treatment intervals to prevent unnecessary flaring of the disease, and this has become recognised as the optimal treatment paradigm with rituximab (2).

Therefore BMS ask the AG to use a re-treatment interval for rituximab of not more than 6 months in the BRAM.

4. The ACD recommends the use of the anti-TNF switching in the context of research only, but not abatacept. The AC explains this by citing the lack of clinical effectiveness data for the anti-TNFs at this stage in the treatment pathway, and the resulting uncertainty in the ICERs (Incremental Cost Effectiveness Ratio). However, they acknowledge the robustness of the available data for abatacept. BMS believes that this is a discriminatory recommendation for abatacept and is also a disincentive for research and innovation. Therefore, BMS asks the AC to recommend abatacept for treatment of RA, without the restriction on use in the context of research.

Furthermore, the BRAM generates similar ICERs for abatacept and the anti-TNFs, all of which are in areas where the anti-TNFs, adalimumab and infliximab have been recommended in earlier appraisals (TA130). In addition, recent data from the golimumab (another anti-TNF) GO-AFTER study indicates that the effectiveness of the use of a second anti-TNF may be reduced.

Therefore BMS asks the AC to recommend abatacept for patients with RA after anti-TNF failure in line with new, evidence based European treatment guidelines from EULAR to be published in Annals Rheumatic Diseases in April 2010.

5. The BRAM insists on using a clinical effectiveness that is too high for conventional DMARDs (in both, the reference case and its scenario analyses) when used after the failure of an anti-TNF. This is in contrast to the findings of the British Society for Rheumatology Biologics Register (BSRBR), who report that conventional DMARDs produce no further HAQ score improvements (5).

The AG may argue that these data come from a non-randomised dataset. However, BMS considers that non-randomised and observational data are able to produce a robust analysis, if there is a lack of randomised data. Furthermore, as pointed out by Professor Rawlins in his Harveian Oration delivered at the Royal College of Physicians of London:

'RCTs, long regarded as the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of "hierarchies" of evidence is inappropriate; and hierarchies, themselves, are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base'.

Therefore BMS ask the AC to accept the BSRBR as an appropriate data source, and the AG to use a 0-HAQ-multiplyer for conventional DMARDs in the BRAM.

In conclusion BMS asks the AC to reconsider its draft recommendation and to recommend abatacept for patients with RA.

Detailed comments on the ACD

In response to your invitation to comment, please find our detailed responses to the ACD in the table below.

	ACD extract	BMS Comment
1 Preliminary recommendations		
1.1	Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis: • that has responded inadequately to other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor (TNF) inhibitor, or • who are intolerant of other DMARDs.	The second bullet point is not in line with the scope of this appraisal. In addition it is outside of the license for rituximab (6). Furthermore BMS believe that only recommending rituximab will leave the substantial number of patients who do not respond adequately to a tumour necrosis factor alpha inhibitor (anti-TNF) treatment (approximately 50% [7]) without further treatment options. Rituximab is known to be inadequate therapy for patients who are rheumatoid factor (RF) negative (1).
1.4	The TNF inhibitors adalimumab, etanercept, and infliximab are recommended for the treatment of rheumatoid arthritis after the failure of a previous TNF inhibitor only in the context of research. Such research (including but not limited to clinical trials) should be designed to evaluate the clinical effectiveness of adalimumab, etanercept and infliximab when used sequentially after the failure of a previous TNF inhibitor, in comparison with management strategies that do not include the use of TNF inhibitors.	Abatacept has extensive clinical data proving efficacy in this population, with robust RCT data, and the analyses demonstrating similar cost-effectiveness results to the anti-TNFs. Furthermore, the anti-TNFs have been shown to be associated with dose escalation, something which is not seen with abatacept (21). Despite this, abatacept has not been recommended. BMS requests the Appraisal Committee (AC) reviews this decision. BMS considers recommending anti-TNFs under the restriction of 'research purposes' to be a bizarre disincentive for innovation.
2. Background		

2.8	NICE technology appraisal guidance 130 recommends the TNF inhibitors adalimumab, etanercept and infliximab, each in combination with methotrexate, as options for the treatment of adults with active rheumatoid arthritis who have a disease activity score (DAS28) greater than 5.1 and whose rheumatoid arthritis has failed to respond to at least two conventional DMARDs, including methotrexate.	BSR draft guidelines recommend anti-TNF treatment as an option for patients with active RA who have a disease activity score (DAS28) ≥ 3.2 (8).
3. The technologies		
3.11	The most common adverse events associated with treatment with rituximab include infusion reactions and infection. Contraindications to the use of rituximab include active severe infections (including tuberculosis, sepsis and opportunistic infections), and severe heart failure or severe uncontrolled cardiac disease. For full details of undesirable effects and contraindications, see the SPC.	Rituximab is associated with an increased risk of developing progressive multifocal leukoencephalopathy (PML) and there are currently 60 reported cases (9-11,18).
4.1. Clinical Effectiveness		

4.1.10	The Assessment Group conducted an adjusted indirect comparison of rituximab and abatacept using data from placebo-controlled trials that included similar populations. The analysis suggested no statistically significant differences in response rates between abatacept and rituximab for ACR20 (relative risk 1.12, 95% CI 0.68 to 1.84), ACR50 (relative risk 1.00, 95% CI 0.33 to 2.98) and ACR 70 (relative risk 1.80, 95% CI 0.24 to 13.35).	The BRAM showed that abatacept produced more QALYs in comparison to rituximab; it can therefore be assumed that abatacept is more effective than rituximab (12). Because RA is a long-term disease, the long-term implications and the chronic nature of the disease need to be taken into account. Rituximab is associated with radiographic deterioration whilst on treatment. This has not been shown with either abatacept or the anti-TNFs. Such radiographic deterioration can be translated into a worsening of the HAQ score and should therefore be included in the economic modelling.
4.1.12	Evidence for the influence of the presence of auto-antibodies (that is, rheumatoid factor and anti-CCP status) on effectiveness was available only for rituximab, from the REFLEX trial. The trial reported no statistically significant differences in treatment effect by rheumatoid factor status.	The lower absolute response rates seen in RF negative patients in the REFLEX trial supports the evidence from observational studies and clinical opinion that rituximab is less effective in RF negative patients than in RF positive patients (1,13). In addition, the recently updated Consensus Statement on biological agents (which reviewed evidence from two RA patient populations) concluded that more robust ACR responses were seen with rituximab in RF/anti-CCP positive patients who were DMARD non responders, and in TNF non responders (14). Therefore, the cost-effectiveness analyses for these patients should use conventional DMARDs as the comparator of choice, not rituximab.

4.2 Cost Effectiveness		
4.2.20	The manufacturer assumed that people who discontinued treatment lost the initial effect of treatment. The underlying progression of the disease whilst on treatment was modelled using HAQ score. This was assumed to improve at an annual rate of 0.0729 for those treated with abatacept.	The improvement in HAQ score whilst on treatment with abatacept is based on data from the ATTAIN trial (15). In contrast, rituximab is associated with a radiographic deterioration (6). This deterioration can be translated into a worsening of the HAQ score (16,22-24). Therefore BMS ask the Assessment Group (AG) to incorporate this into their economic modelling.
4.2.22	Sensitivity analyses showed that when it was assumed that the HAQ score progression rates were the same for all biological DMARDs, the ICER for abatacept was £40,534 per QALY gained compared with rituximab, and £27,871 per QALY gained compared with TNF inhibitors.	There is no HAQ deterioration associated with abatacept, whilst there is with rituximab (6,15,16,22-24). BMS therefore ask the AG to incorporate this in their economic modelling.
4.2.24	In addition to the initial response to treatment, the model assumed that underlying disease progressed during treatment. This was modelled by increases in the HAQ score. In the base-case analysis, it was assumed that the HAQ score remains constant for a person treated with a biological DMARD, but increases (worsens) for patients treated with conventional DMARDs or palliative care.	There is no HAQ score deterioration associated with abatacept, whilst there is with rituximab (6,15,16,22-24). BMS ask the AG to incorporate this in their economic modelling.

4.2.25	Re-treatment with rituximab was assumed to occur every 8.7 months.	The re-treatment interval with rituximab has been shown to be 6 months (4). Any re-treatment interval which is ≥ 6 month would need to be accounted for in the economic model with a rebound effect on the HAQ score (20) (in addition to accounting for the underlying radiographic progression). An analysis of responses to a single course of rituximab treatment over 6 months shows maximal efficacy on HAQ-DI at week 16 with a subsequent reduction in efficacy after this (20). BMS asks the Assessment Group to account for this in their economic model.
4.2.26	The base-case analysis showed that for rituximab compared with conventional DMARDs, the incremental QALY gain was 0.96 with an incremental cost of £20,400 giving an ICER of £21,100 per QALY gained.	The reference case in the BRAM model underestimated the true cost of rituximab because it used a hypothetical re-treatment interval of 8.7 months, whereas 6 months would be more reflective of clinical practice (4). Furthermore, rituximab is associated with an underlying disease progression whilst on treatment (6,16,22-24). A comparison of abatacept, or the anti-TNFs, with rituximab is only acceptable in patients who are RF positive, as it has been shown that rituximab is less effective in RF negative patients (1,13). For the analysis of the cost-effectiveness of abatacept in the RF negative population, comparison to conventional DMARDs should be used (instead of rituximab). BMS ask the AG to incorporate this into their modelling.
4.2.27	Scenario analyses were undertaken to explore the impact of varying single assumptions in the model.	These sensitivity analyses explored only the impact of single assumptions, not their combined impact. BMS asks the AG to present revised sensitivity analyses to the AC.

4.2.28	Assuming that there was underlying progression of disease modelled as an increase in HAQ score of 0.03 per year whilst on biological DMARDs increased the ICERs for the comparison with conventional DMARDs. Assuming conventional DMARDs were no more effective than placebo, this reduced the base-case ICERs for the comparison with conventional DMARDs to £28,100 per QALY gained for adalimumab, £31,100 per QALY gained for etanercept, £28,800 per QALY gained for infliximab, £16,300 per QALY gained for rituximab and £32,100 per QALY gained for abatacept.	There is no HAQ progression associated with abatacept, whilst there is with rituximab (6,15,16,22-24). BMS ask the AG to use this data in their economic modeling. Conventional DMARDs used after an inadequate response to methotrexate and an anti-TNF have been shown not to lead to any further improvement in HAQ score (5,17). Therefore BMS ask the AG to use a 0-HAQ-multiplyer for conventional DMARDs in the BRAM.
4.3 Consideration of the Evidence		
4.3.2	The Committee heard from clinical specialists that the pathway of care following the failure of treatment with a TNF inhibitor depends on the individual person's responses to therapies, the clinical experience of the physician and the person's preference.	RA is a complex disease which requires a differentiated and individualised treatment approach. Currently there are only very few therapeutic options available for patients who have failed a series of treatments, including at least two conventional DMARDs and one anti-TNF. The current ACD will further limit the already scarce treatment options available. Furthermore, the only fully recommended treatment option (rituximab) is associated with uncertain treatment outcomes in RF negative patients, as well as with the risk of developing (9-11,18). BMS ask the AC to recommend abatacept.

4.3.3	Experts stated that people with sero-negative antibody status may be less suitable for treatment with rituximab.	The lower absolute response rates seen in RF negative patients on rituximab in the REFLEX trial reinforces evidence from observational studies and clinical opinion that rituximab is not as effective in RF negative patients than in RF positive patients (1,2,13). Therefore, cost-effectiveness analyses for these patients should use conventional DMARDs as the comparator of choice, not rituximab.
4.3.4	The Committee understood that these changes in the management of rheumatoid arthritis limited the generalisability of data from the British Society for Rheumatology Biologics Register.	The treatment paradigm for RA has indeed changed in recent years towards a more aggressive and earlier therapy. However, in the absence of better data sources, the British Society for Rheumatology Biologics Register (BSRBR) should be used to inform any economic analyses.
4.3.6	The Committee heard from clinical specialists that for conventional DMARDs, the proportion of people whose condition responded to sequential treatments was reduced as the number of treatments received increased.	Conventional DMARDs used after an inadequate response to methotrexate and an anti-TNF have not been demonstrated to lead to any further improvement in HAQ score (5,17). Therefore BMS ask the AG to use a 0-HAQ-multiplyer for conventional DMARDs in the BRAM.
4.3.7	The Committee concluded that both treatments had been shown to be clinically effective in comparison with placebo, but that one treatment had not been shown to be more effective than the other.	Rituximab is associated with a radiographic deterioration (6). This deterioration can be translated into a worsening of the HAQ score (16,22-24). The BRAM shows that abatacept produces more QALYs in comparison to rituximab, therefore it can be assumed that abatacept is more effective than rituximab (12).

4.3.9	The Committee concluded that there was insufficient evidence to make differential recommendations for subgroups based on auto-antibody status.	The ACD acknowledges (section 4.1.12) that, in the REFLEX trial, absolute response rates were lower in both the rituximab and the placebo groups for patients who were RF negative compared to those who were RF positive. The ACD also acknowledges that when participants were stratified according to both RF and anti-CCP status, the data suggest a greater treatment response in those who were RF or anti-CCP positive than in those who were negative for RF and anti-CCP. However, the AG noted that this retrospective analysis should be treated with caution. BMS believes, these data highlight that rituximab is not an optimal treatment option for patients who have seronegative RA. This is further supported by the findings of the trials studying rituximab for the treatment of RA after the failure of conventional DMARDs (i.e. MIRROR, SERENE) (1). In a combined analysis of these studies, seropositive patients were 2–3 times more likely to achieve ACR responses compared with patients seronegative for both autoantibodies. In the DANCER study, rituximab was even less effective than placebo when administered to patients who have seronegative RA. These data are further supported by clinical opinion (2). BMS acknowledges that there may not be sufficient data available from randomised clinical trials (RCTs) for rituximab in TNF-inhibitor failure patients to be used in the BRAM, but asks the AC to acknowledge the high degree of uncertainty regarding the effectiveness of rituximab in seronegative RA.

4.3.10	Overall, the Committee concluded that, on the basis of clinical opinion, the effect of conventional DMARDs in people for whom a TNF inhibitor had failed was likely to be small, but the relative effect in comparison with biological treatments was not currently quantifiable.	Conventional DMARDs used after an inadequate response to methotrexate and an anti-TNF have been shown not to lead to any further improvement in HAQ score (5,17). BMS asks the AG to use a 0-HAQ-multiplyer for conventional DMARDs in the BRAM. In the absence of better data sources, the British Society for Rheumatology Biologics Register (BSRBR) should be used to inform any economic analyses.
4.3.11	In summary, the Committee noted that apart from the randomised controlled trials of rituximab and abatacept, the available evidence on the effectiveness of treatment with a biological DMARD after the failure of a TNF inhibitor was mainly derived from observational studies with short follow-up periods that included relatively small numbers of people.	The ACD recommends the use of anti-TNFs for research only, but not abatacept. The BRAM generates similar ICERs for abatacept and the anti-TNFs versus conventional DMARDs. The AC explains this with the lack of clinical effectiveness data for the anti-TNFs at this stage in the treatment pathway, and the resulting uncertainty in the ICERs, whilst they acknowledge the robustness of the available data for abatacept. BMS believes that this is a differential recommendation for abatacept and disincentives research and innovation. In addition, recent data from the golimumab (a further anti-TNF) GO-AFTER study indicates that the effectiveness of the use of a second anti-TNF maybe lower.

4.3.14	The Committee was aware that no head-to-head evidence existed comparing all the biological DMARDs, and as a result some models derived relative treatment effect from indirect comparisons. The Assessment Group reported that it considered the use of data from populations beyond the scope of the appraisal to complete an indirect comparison as inappropriate due to the variability of the studies from which the data were taken. The Committee considered that the use of non-randomised comparisons could affect the robustness of the results. However, it accepted that the evidence base available for the sequential use of biological DMARDs did not currently allow for a robust analysis of the relative treatment effect.	In the absence of better data sources, the BSRBR should be used to inform any economic analyses. BMS considers that the use of non-randomised and observational data are able to produce a robust analysis when there is a lack of randomised data. Furthermore, Professor Rawlins stated in his Harveian Oration delivered at the Royal College of Physicians of London (19) *'Randomised controlled trials (RCTs), long regarded at the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of "hierarchies" of evidence is inappropriate; and hierarchies, themselves, are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base'* A consistent use of non-randomised data should be used for all comparators. For example, currently the BRAM model assumes efficacy for DMARDs post anti-TNF failure, but is reluctant to use effectiveness data from non-randomised studies on abatacept that suggest maintenance/improvement in HAQ score over time. BMS ask the AC to consider the quality of the non-randomised data provided and that non-randomised data are used consistently across comparators.

4.3.17	The Committee noted that one of the analyses (from Bristol-Myers Squibb) had assumed that abatacept delayed progression more than the other biological DMARDs. The Committee was not persuaded that this was supported by the evidence. The Committee agreed to base its discussions on the ICERs which assumed no progression of disease for patients during treatment with the biological DMARDs, but was not persuaded that this assumption fully reflects the disease process.	The improvement of the HAQ score whilst on treatment with abatacept is based on data from the ATTAIN trial (15). In contrast, rituximab is associated with a radiographic deterioration (6). This deterioration can be translated into a worsening of the HAQ score (16, 22-24). Therefore BMS ask the Assessment Group (AG) to use these data in their economic modeling.
4.3.19	The Committee noted that the Birmingham Rheumatoid Arthritis Model incorporated the time to repeat treatment as 8.7 months in the base case, basing this estimate on Roche's submission. On the basis of the clinical specialists' advice, the Committee assumed that treatment with rituximab would occur, on average, less frequently than every 6 months.	The BRAM still uses a treatment interval of 8.7 months - this is too long for rituximab. Recent market research showed an average re-treatment interval with rituximab of 5.9 months (4). This is supported by clinical opinion (2), which states that although longer treatment intervals were common historically, physicians now use shorter 6 month re-treatment intervals to prevent unnecessary flaring of the disease, and this has become recognised as the optimal treatment paradigm with rituximab (2). Therefore BMS ask the AG to use a re-treatment interval for rituximab of not more than 6 months in the BRAM.

4.3.21	The Committee concluded that an analysis that assumed the effect of conventional DMARDs to be no more effective than that of placebo was not plausible, but accepted on the basis of clinical specialists' testimony that the base case assumption of a reduction by 50% may be an underestimate of the reduction in effect of conventional DMARDs, therefore overestimating the ICERs in the Assessment Group's base case analysis.	Conventional DMARDs used after an inadequate response to methotrexate and an anti-TNF have been shown not to lead to any further improvement in HAQ score (5,17). Therefore BMS ask the AG to use a 0-HAQ-multiplyer for conventional DMARDs in the BRAM.
4.3.22	The Committee then examined the Assessment Group's scenario analysis, which assumed a time to re-treatment of 6 months. It noted this assumption increased the ICER from £21,100 to £32,600.	The BRAM still uses a treatment interval of 8.7 months - this is too long for rituximab. Recent market research showed an average re-treatment interval with rituximab of 5.9 months (4). This is supported by clinical opinion (2), which states that although longer treatment intervals were common historically, physicians now use shorter 6 month re-treatment intervals to prevent unnecessary flaring of the disease, and this has become recognised as the optimal treatment paradigm with rituximab (2). Therefore BMS ask the AG to use a re-treatment interval for rituximab of not more than 6 months in the BRAM.

4.3.24	The Committee considered that most of the economic models showed that in comparison with rituximab, the ICERs for abatacept were either very high (above £100,000 per QALY gained in the Assessment Group base case) or abatacept was dominated by rituximab (that is, rituximab was both more effective and less costly). The analysis by Bristol-Myers Squibb which produced an ICER of £20,438 per QALY gained assumed an improvement in HAQ score of 0.013 per year during treatment with abatacept. When the same rate of HAQ score progression was assumed for abatacept as for the other biological DMARDs in the base case analysis (a worsening of 0.012 per year), the ICER increased by £40,534 per QALY gained. The Committee therefore concluded that abatacept when used as an alternative to rituximab after the failure of a previous TNF inhibitor would not be a cost-effective use of NHS resources.	The BRAM shows that abatacept produces more QALYs in comparison to rituximab, and so it can be assumed that abatacept is more effective than rituximab (12).Therefore the statement that rituximab is more effective than abatacept is not true. The improvement in HAQ score whilst on treatment with abatacept is based on data from the ATTAIN trial. In contrast rituximab is associated with a radiographic deterioration. This deterioration can be translated into a worsening of the HAQ score. Therefore BMS ask the AG to use this data in their economic modelling, and that the AC base their decision on the revised analyses.

4.3.26	The Committee concluded that it would be appropriate to recommend the use of adalimumab, etanercept and infliximab after failure of a TNF inhibitor only in the context of research.	Abatacept has extensive clinical data proving efficacy in this population, with robust RCT data. The analyses demonstrate similar cost-effectiveness results to the anti-TNFs. Furthermore, unlike abatacept, anti-TNFs have been shown to be associated with dose escalation (21). Despite this, abatacept has not been recommended. BMS requests the AC reviews this decision. Recommending anti-TNFs under the restriction of 'research purposes', would seem to be a disincentive for innovation.

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