**Response to:**

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

# Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs

**Prepared by:**

**Bristol-Myers Squibb Pharmaceuticals Limited**

**20th April 2011**


**CONFIDENTIAL VERSION**

**Response to the Appraisal Consultation Document: Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs**

**Confidential information is highlighted and underlined, e.g.** [redacted]

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| Approved Name of Medicinal Product: | abatacept |
| Brand Name: | Orencia |
| Company: | Bristol-Myers Squibb Pharmaceuticals Ltd |
| Submitted by: | [redacted] |
| Position: | Associate Director Health Economics and Outcomes Research |
| Date: | 20 April 2011 |

Bristol-Myers Squibb (BMS) welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) relating to the ongoing appraisal of abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs.

BMS do, however, disagree with the preliminary recommendation of the ACD not to recommend abatacept, and our reasons for this are that the Appraisal Committee has:

- dismissed BMS' use of the HAQ score, preferring us to use the DAS28;
- penalised BMS for using a non-linear approach to map HAQ scores to EQ-5D utility values, an approach widely accepted historically;
- assumed that patients will experience a decreased response to abatacept over time, when there is no evidence whatsoever to support such an assumption;
- suggested that BMS should use a much shorter time horizon than is implied by the natural history of the disease, or that used in assessing comparator products;
- dismissed abatacept as a valid treatment for the small number of patients who are contraindicated to TNF inhibitors, especially as these patients have no other therapeutic alternatives;
- not only suggested that needle phobia isn't different from an infusion, but also that it isn't an issue for patients, contrary to the evidence given by patients themselves at the appraisal committee hearing.

These elements have led to an ACD which is both unfair and perverse.

These concerns are discussed in more detail below.

## 1. Modelling HAQ score instead of the DAS28

Historically, the HAQ score has been used and accepted during numerous technology assessments for treatments for RA. Furthermore, whilst the DAS 28 is more often used in clinical practice than the HAQ, and may give a better day to day clinical picture of the disease, the HAQ allows superior mapping to utilities. Indeed, HAQ has proven to be more predictive of RA disease progression than any other measure of response criteria (Wolfe et al. 1991, Callahan et al. 1992, Pincus et al. 1994, Fries et al. 1996). This has been well established, and used extensively for a number of years (Barton et al. 2004).

It should be emphasised that there are two ways of calculating DAS score, (1) by using the ESR and (2) by using CRP while, in contrast, there is only one method by which to measure HAQ. This means that the DAS 28 scores very much depend on the chosen method of measurement (which is not always reported) and so will affect associated utilities in an inconsistent way (Sheehy et al. 2011).

The validity of HAQ based modelling has been discussed on numerous occasions in the early appraisals of RA, resulting in the consensus that such an approach is the preferred method. Indeed, the Technology Assessment Group (TAG) used this methodology in both TA130 (2007) and TA195 (2010). BMS believe that it is unfair of the AG to suggest that BMS should have set a precedent by assessing abatacept's cost effectiveness using the DAS 28. BMS used established methodology which had previously been accepted by NICE, in good faith, and feel it is both perverse and unjust for the AG and the AC to dismiss this approach.

**In summary, BMS asks the Appraisal Committee to accept that HAQ based modelling is the correct and well accepted approach to modelling RA**

## 2. Approach to mapping HAQ score to utility

The AC questioned whether using a non-linear approach to map HAQ scores to EQ-5D utility values was biased in favour of abatacept. BMS refutes this suggestion. This approach has been accepted by previous Appraisal Committees and become a widely accepted methodology. For example, in the appraisal leading to the publication of TA 130 (section 4.3.10 pg 27);

*"The Committee was aware of the limitations of using HAQ scores as a basis for estimating health-related quality of life in patients with RA. Namely that the HAQ is a measure of functional disability, which fails to*

*capture the psychological and pain elements of quality of life associated with RA. In addition, the Committee noted that the HAQ scoring system may be an insensitive measure of small changes in health-related quality of life and may have a non-linear relationship to utility scores. The Committee noted that HAQ had been used as a basis for calculating utility across all the economic models, and while noting its limitations, accepted that it was the best means of estimating utility for the purposes of the economic analysis given the available data".*

This approach has also been described in the literature (Barton et al. 2004)

*"However, it is possible that a better fit can be obtained from a non-linear relationship".*

BMS considers it perverse and unfair to compare abatacept against recommended products that have been approved utilising agreed methodologies, and then to refuse abatacept because BMS used those same methodologies. In light of the above evidence, it is unjustifiable for the AC to suggest an alternative methodology be used, based solely on its effect on the resultant ICER. The accepted approach is to choose a scientific methodology based on its own merit in order to produce a valid ICER.

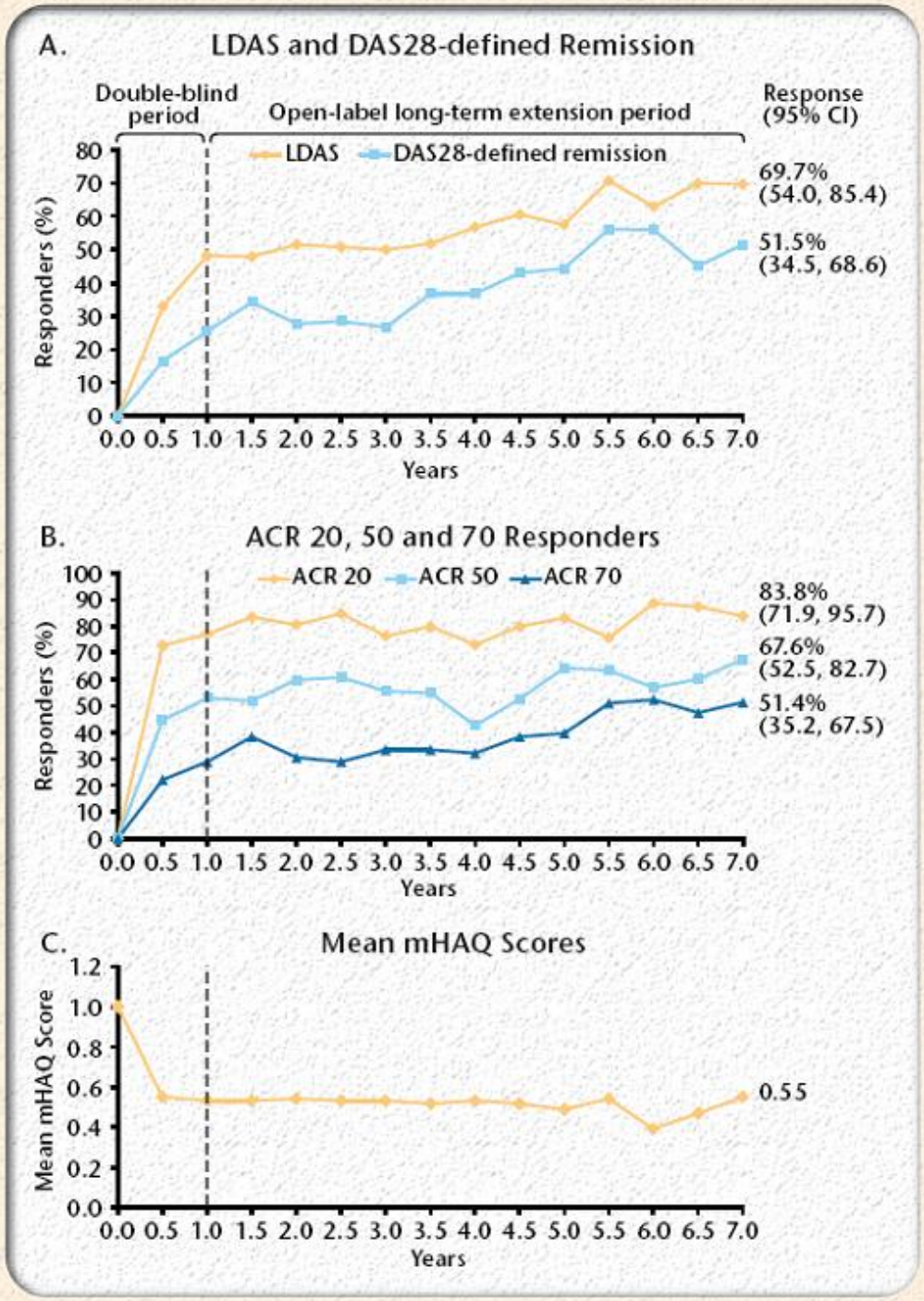
**In summary, BMS asks the Appraisal Committee to accept that using a non-linear approach to map HAQ scores to EQ-5D utility values is unbiased and methodologically correct**

### 3. Decrease of abatacept effect over time

The Committee considers that it is biologically plausible that patients treated with abatacept could have a decreased response to the agent over time, given the experience from the other biologic DMARDs. However, it offers no data to support this assumption and BMS considers the AC's assumption to be flawed. It is unlikely that abatcept, which is a human fusion molecule, could cause neutralising antibody production, which is the biological phenomenon that causes reduced efficacy in a biologic (and which necessitates dose escalation).

Indeed, data from the abatacept clinical studies show that such a phenomenon does not occur. In abatacept treated patients the immunogenicity rate is very low, and there has been no report showing that it translated into a loss of efficacy (Haggerty et al. 2006, Haggerty et al. 2007). Clinical trials experience has shown a sustained efficacy over 7 years (see Figure below) (Westhovens et al. 2009a) and a high retention rate of abatacept in the long-term extension of a number of trials (Westhovens et al. 2009, Kremer et al. 2009).

## Figure 3. Disease Activity, Clinical Efficacy and Physical Function over 7 Years of Abatacept Treatment




Data are based on all patients originally randomized to 10 mg/kg abatacept who entered the long-term extension, with data available at the visit of interest (as-observed analysis); DAS28 (C-reactive protein [CRP])-defined remission=DAS28 <2.6; LDAS=DAS28 (CRP) ≤3.2; LDAS=Low Disease Activity State; CI=confidence interval; mHAQ=modified Health Assessment Questionnaire

**(Taken from Westhovens R. et al 2009)**

Furthermore, as highlighted in the EPAR document, abatacept has a similar retention rate to etanercept, and a higher retention rate than adalimumab (Variation Assessment Report EMA/361627/2010).

Real-life data from clinical trials also support the contention that dose escalation occurs with infliximab. Ariza-Ariza et al. (2007) showed that of 5,862 patients who received infliximab, 53.2% experienced dose increases. Similarly, Simons et al. (2009) showed that 16% of patients receiving infliximab (from a 2,865 patient cohort) experienced dose increases, and decreases between dosing intervals. In contrast, in an 1,014 abatacept patient cohort, such dose escalation did not occur, with the patients receiving consistent doses and infusion intervals over time.

BMS understand why the AC has used other biological DMARDs on which to base their assumption, because it is a recognised phenomenon with the monoclonal antibodies. For example, because it is a chimeric monoclonal antibody with some murine amino acid sequences, infliximab does have a propensity to cause neutralising antibody formation (Ebert et al. 2008) which results in reduced response over time (1 year data: Schiff et al. 2008, Schiff et al. 2009). In practice, this will necessitate a dose escalation of infliximab in a third or more of patients treated (Rahman et al. 2007).

Data from long-term extension studies with abatacept show an incremental proportion of patients achieving each of the categorical ACR response rates (20, 50 and 70%) over time and, furthermore, progressively better radiological evidence of structural inhibition (Genant et al. 2009, Genovese et al. 2009, Kremer et al. 2009, Westhoven et al. 2009b). These observations are very likely to represent true improvement because although the data is "as-observed", the retention rate on drug is remarkably high at 88.9% during the double blind period of the AIM study and 70.4% during the open label period (Kremer et al. 2006 and 2009). These important observations are likely to reflect the unique mechanism of action of abatacept as a co-stimulation blocker with tolerance induction over time.

BMS therefore considers the AC assumption, and extrapolation of the biologic DMARD/infliximab issues to abatacept, to be both erroneous and perverse.

**In summary, BMS asks the Appraisal Committee to accept that, unlike other biologic DMARDs, abatacept does not have a decreased effect over time**

## 4. Time horizon of model

The AC discussed the time horizon of the model, and the effect of using a shorter time horizon (from lifetime to 5 years) had on the model. The onset of the disease is generally between 40-60 years of age although it can occur at any age (NRAS 2011). There are also around 12,000 children

under the age of 16 with the juvenile form of the disease. Thus, it should be appreciated that rheumatoid arthritis is a chronic disease, which is a lifetime sentence for the sufferer. This means a lifetime time horizon for the model should be used.

The NICE Methods Guide (paragraph 5.2.14 page 33) states:

*"Many technologies have impacts on costs and outcomes over a patient's lifetime. This is particularly the case with treatments for chronic diseases. In such instances, a lifetime time horizon for clinical and cost effectiveness is appropriate".*

Therefore BMS feels the AC decision to limit the time horizon to just 5 years is clinically erroneous, medically implausible and leads to flawed results. BMS further believes that it is perverse in light of the evidence available.

**In summary, BMS asks the Appraisal Committee to accept that a lifetime time horizon model is appropriate**

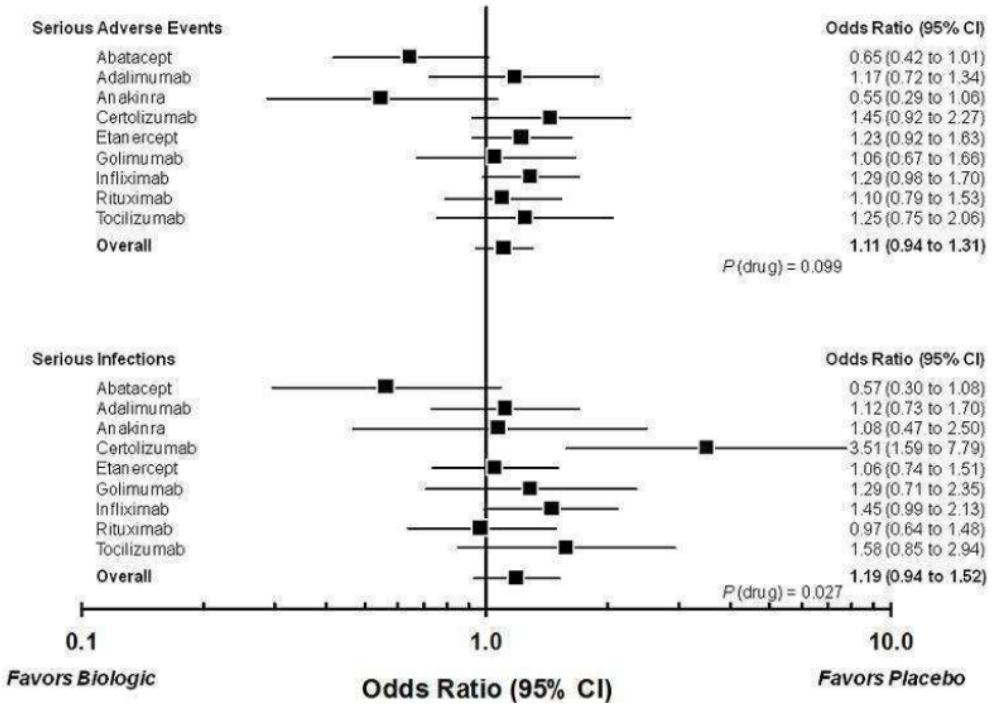
## 5. Contraindication to TNF inhibitors

The Committee heard from the clinical specialists that abatacept offered a viable alternative for patients for whom there are contraindications to a TNF inhibitor. BMS agrees with this assessment and the potential for abatacept.

Because of its different mode-of-action, there may be subpopulations in whom abatacept may provide specific benefits, and for whom there are no alternative therapies. For example, abatacept is not contraindicated for moderate to severe heart failure, in contrast to infliximab. TNF inhibitor therapy is not advised for patients with interstitial lung disease (ILD) as it increases the risk of infections (Perez-Alvarez et al. 2011, Dixon et al. 2010). Rituximab has been associated with a negative impact on pulmonary fibrosis while (Leon et al. 2004, Park et al. 2010, Reynolds et al. 2009, Wagner et al. 2007), in contrast, abatacept may be used in patients with ILD, as it is not associated with any negative outcomes in these patients.

A recent independent meta-analysis (Singh et al. 2011) supported abatacept's favourable safety and tolerability profile, specifically in regard to serious infections. This is also supported by EPAR 2010 (Variation Assessment Report EMA/361627/2010)

**Figure 2. Forest plots: serious adverse events and serious infections**




**(Taken from Singh et al. 2011)**

Furthermore in RA patients with prior demyelinating episodes or co-existing multiple sclerosis (MS), therapy with a TNF inhibitor is associated with a worsening of the symptoms of MS (Mohan et al. 2011, Ruiz-Jimeno et al. 2006, Sukal et al. 2006, Enayati et al. 2005, Thomas et al. 2004). Expert clinicians[1] have expressed a need for biologics with alternative mechanisms of action for this group of patients who currently who have no other options under NICE guidance.

As highlighted by the clinical specialists, such contraindicated populations are likely to be small. BMS consider the AC have exceeded its remit by dismissing abatacept as a valid treatment for these patient groups, especially as these patients have no further therapeutic alternatives under the current NICE guidelines.

[redacted]

The AC was aware of a potential additional decision problem expressed by the clinical specialists which compared abatacept with conventional DMARDs, against which abatacept has been shown to be cost effective. Therefore the AC should recommend abatacept as an alternative treatment option in patients with RA who are contraindicated to TNF inhibitors.

**In summary, BMS asks the Appraisal Committee to recommend abatacept as a first line biologic option for patients with RA**

## 6. Needle phobia

The AC concluded that people with subcutaneous needle phobia would have the same problem with intravenous therapy. However, they offer no data to support this conclusion and the position is not as simple as this – phobia to needles precluding subcutaneous self administration can be overcome with the option of IV administration carried out by a third party. For every patient who is able to receive subcutaneous delivery, there are likely to be others for whom such administration limit the acceptability of this treatment (Scarpato et al. 2010). Such patients deserve an alternative therapeutic option. Needle phobia remains a significant problem for some patients, as the patient groups represented at the AC meeting testified. At present, the only NICE approved alternative is infliximab which, as discussed above, is associated with dose-escalation and reduction in efficacy over time.

**In summary, BMS asks the Appraisal Committee to provide abatacept as an alternative therapeutic option to subcutaneous administration**

**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 |
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| **Page 3 2.1** | Abatacept (Orencia, Bristol-Myers Squibb) is a selective T-cell co-stimulation modulator that blocks a co-stimulatory signal required to activate T-cells. | Abatacept shows an innovative mode of action. It is a T-cell modulator that blocks the co-stimulation mechanism that activates T-cells, a pivotal step in the RA inflammatory cascade and subsequent joint destruction. This upstream modulation of T-cells occurs early in the inflammatory cascade. Therefore, downstream inhibition of inflammatory cell proliferation and cytokine release supports the use of abatacept early in the development of RA to maximize its benefits. This mechanism of action also explains the clinical data generated in the ATTEST study (Schiff et al. 2008 and 2009) where ACR responses tended to be faster with infliximab +MTX than abatacept + MTX in the first 3 months. However, by 6 months, the difference between the two active agents and placebo were similar. Importantly, clinical data show that efficacy with abatacept +MTX has been sustained in the majority of patients for up to 7 years, with high retention rates. |
| **Page 18 3.31** | The ERG noted that the base case in the model included escalating the dose of infliximab and etanercept if required, but not of abatacept. | The Committee discussed the issue of dose escalation of infliximab and have questioned whether the model used by BMS should also include dose escalation of abatacept. To clarify, dose escalation due to reduced response to infliximab over time (due to antibody formation against the murine component of infliximab, reducing the effective active agent in any given dose) is a recognised phenomenon (van Vollenhoven et al. 2004, Edrees et al. 2005, Ariza-Ariza et al. 2007, Blom M et al. 2010). Indeed, it is accepted |

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| | | as such by infliximab's manufacturers, their SPC stating *"If a patient has an inadequate response or loses response… consideration may be given to increase the dose step-wise…",* and has been documented by Singh et al. (2011) in the recent Cochrane review (see Figure above).<br><br>Importantly, due to abatacept being a human fusion molecule, such a phenomenon is extremely unlikely to occur with this agent, and to date there are no abatacept data suggesting this position to be invalid. Thus, BMS consider their original stance to consider dose escalation for infliximab, but not for abatacept infliximab, to be valid. |
| **Page 16 3.26** | The ERG noted that people in the included trials had not had rheumatoid arthritis for as many years, or had taken as many conventional DMARDs as people in UK clinical practice starting a biological DMARD. | The Committee agree that abatacept is clinically effective, as do the Clinical Experts. In their report the AG outline the clinical efficacy end points used in the clinical trials, and discuss the levels of improvement in the HAQ scores and DAS scores which are accepted as being clinically meaningful.<br><br>However, perversely, in their response the AG suggested that this substantial body of evidence, from clinical trials which were performed to internationally accepted standards, and which have been accepted by a number of different regulatory bodies, could be flawed. Their hypothesis is that the population in the studies did not reflect the actual rheumatoid population.<br><br>The AG present no actual evidence as to what this "real world" population might be, or how they differ from the abatacept clinical trial population with regard to symptoms, disease status, posology and outcomes, or whether any subgroups from the abatacept trial |

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| | | population might reflect their preferred population. To disregard data from regulatory accepted clinical trials on the basis of an unsubstantiated hypothesised difference between populations would seem to be beyond the Committee's remit. |
| **Page 22 4.3** | The Committee heard that the management of rheumatoid arthritis has been changing in line with NICE guidance, and that clinicians start treatment with conventional DMARDs or TNF inhibitors sooner after a person's diagnosis of rheumatoid arthritis than in the past. | Interestingly, the ACD report highlights the Expert Opinion that current clinical practice means that patients are receiving biological DMARDs much sooner than was previously the case. If one accepts the AG opinion alluded to in Paragraph 3.26 *(point above)* one might reasonably consider that the abatacept clinical trial population does actually reflect those patients in whom these treatments would be used in current clinical practice |
| **Page 16 3.26** | Therefore, although the evidence submitted largely reflected the decision problem defined in the scope, the ERG considered that the difference between the populations may translate to a smaller actual benefit from abatacept in UK clinical practice than was observed in the trial populations. This was because people with disease of longer duration or who have received a larger number of treatments may respond less well than people with disease of shorter duration or who have received fewer treatments. | However, ff one does not accept the AG argument (Paragraph 3.26), it should be noted that in the abatacept clinical trials the average duration of RA was 8 years prior to abatacept treatment. This duration, and associated disease progression, would imply that abatacept was assessed in a more refractory (challenging) population than is currently treated in clinical practice, yet was still shown to be clinically effective. |
| **Page 18 3.33** | The ERG highlighted that although based on the endpoints of the key trials, an improvement of 0.3 in HAQ score may not reflect a clinically meaningful improvement. | The AG suggested that the accepted clinically relevant change in HAQ score (0.3) was not clinically meaningful**.** The threshold of 0.3 relies on previous published work, a point made by BMS in the responses to the ERG report. The AG present no evidence as to what they consider the level of change in HAQ scores should be in |

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| | | order to be clinically meaningful. At the TAC, the clinical experts suggested that 0.3 might actually be rather conservative (something with which BMS agree), with a level of 0.19-0.22 being cited as clinically meaningful (Goldsmith et al. 1993, Wells et al 1993, Kosinski et al. 2000, Cohen et al. 2003). Indeed, to compound their misunderstanding of the clinical assessment, the AG use 0.5 (considered "normalisation" by clinical experts) in their economic calculations. One can only assume that the AG thought this to be clinically meaningful; however it is not supported by evidence/data. Typically, registration biologic clinical trials have used 0.22 or 0.3, although 0.3 is considered the more robust by clinical experts. |
| **Page 23 4.4** | The Committee heard from the manufacturer that it used HAQ for consistency because previous submissions for other NICE technology appraisals related to rheumatoid arthritis also used HAQ. The Committee considered that consistency had merits, but making a decision based on clinically meaningful outcomes was more. important. The Committee expressed a preference for DAS28 as an outcome measure in economic models of rheumatoid arthritis, noting also that clinicians decide to stop or change treatment based on DAS. | The HAQ score has been used and accepted in numerous Appraisal Committees as the preferred assessment criteria to be used in the economic modelling. While DAS 28 had been used in abatacept clinical trials (as well as ACR), and clearly supports the clinical efficacy of abatacept, the AG suggest that BMS should have set a precedent by assessing abatacept's cost effectiveness using the DAS 28. If BMS had used DAS 28 instead of HAQ we presume the assessment group would also have found this equally wanting due to lack of precedent.<br><br>Indeed, if the HAQ was inappropriate, it could be considered perverse that the Committee limit themselves to a single alternative scoring system to the HAQ. Abatacept has been shown to provide statistically significant improvements in RA patients with inadequate response to methotrexate in SF-36 across a range of health related quality of life (HRQoL) domains including: physical function; fatigue in all 8 domains of the SF-36; and the physical |

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| | | and mental component summaries (PCS and MCS) (Russell et al. 2006). Abatacept is also associated with substantive and significant improvements in the ability of patients to participate in their usual activities using the validated Activity Participation Questionnaire (APaQ) (Li et al in press). Similar significant improvements have also been found with abatacept treatment using other quality of life scales such as the sleep disturbance scale of Medical Outcomes Study Sleep (MOS-sleep) measure (Wells et al. 2010). |
| **Page 24 4.5** | Lastly, the Committee was aware of a potential additional decision problem expressed by the clinical specialists, which compares abatacept with conventional DMARDs, but only in the subpopulation of people for whom clinicians consider TNF inhibitor treatment inappropriate because of a contraindication. | BMS agree with this assessment. Unfortunately, as highlighted by the Committee, such a population is likely to be very small – indeed the BMS data base on such contraindicated patients is very small – so the opinions of clinical experts will have to suffice in lieu of firm data. |
| **Page 25 4.7** | The Committee noted that there was no significant difference between infliximab plus methotrexate compared with abatacept plus methotrexate, but also noted that although the ATTEST study included separate arms for abatacept, infliximab and placebo, this study was not powered to detect statistically significant differences between abatacept and infliximab. | It is important to recognise abatacept has been shown to be an alternative to infliximab, albeit with specific advantages with regards to clinical response over time and a favourable safety profile. Abatacept and infliximab were studied individually versus placebo + MTX in the same study. However as the study protocol was the same for both sets of groups they both reduced disease activity to the same extent at 6 months. However, after 1yr, patients on infliximab + MTX were switched to abatacept, with the majority of patients experiencing incremental improvements in the disease activity status. Indeed EPAR (Variation Assessment Report as adopted by the CHMP EMA/361627/2010)<br>states abatacept has a similar short term efficacy profile but more favourable long-term efficacy. In addition, the recent Cochrane |

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| | | meta-analysis (Singh et al. 2011) found that abatacept was associated with fewer serious adverse events and fewer serious infections compared with the other biologics |
| **Page 18 3.32** | In the base-case analyses, the manufacturer assumed that people do not share vials and generally go to hospital to receive intravenous infusions. The ERG stated that it may be possible for larger hospital units to share vials. | The Committee also discussed the vexed topic of infliximab vial sharing. BMS' position is that there are no hard data on this issue. The discussions at the TAC showed that clinical opinion is not based on firm evidence. There are no data to show that such a practice is widespread, and one which is formally supported by hospital, clinical and pharmacy practice. Indeed, it was also suggested by one of the clinical experts that "rounding up" of infliximab vial content might just as easily occur. It would seem perverse to base clinical practice (as reflected in the model) on hypothetical discussions at best , and "bad practice" at worst. |
| **Page 22 4.2** | Clinical specialists and patient experts emphasised the importance of having a choice of treatment for people whose disease has not responded adequately to initial treatment with conventional DMARDs. The clinical specialists expressed that the choice of a biological agent with a mechanism other than inhibiting TNF was especially important for people who cannot be treated with a TNF inhibitor. | Importantly, the Clinical Experts consider choice to be paramount. Indeed, BMS consider it to be essential offer the choice of an alternative biologic to those patients in whom infliximab has been shown to be ineffective, or in whom conventional TNF inhibitor agents are contraindicated, **as these patients really do not have any other treatment option.** Rituximab, the only other biological of possible choice, has no data to support its use in this situation, and is anyway not licensed as a first line biologic therapy.<br><br>Finally, in a recent Cochrane review (Singh et al 2011) abatacept was shown to be associated with a significantly lower risk of serious adverse events compared with most other biologics used in RA. Indeed, abatacept was considered significantly less likely than infliximab to (a) be associated with serious adverse events, (b) serious infections and (c) result in withdrawals due to adverse |

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| | | events. Because of these recent Cochrane findings it would seem perverse, given that the ATTEST study (Schiff et al 2008 and 2009) showed abatacept and infliximab reduced disease activity to the same extent, that abatacept should not be available to RA patients in whom infliximab has proved inadequate – whether due to reduced clinical effectiveness resulting in dose escalation, or due to the increased likelihood of side effects.<br><br>In summary, as confirmed by Expert Opinion, abatacept should be available to be used by patients who cannot be treated by a TNF inhibitor. It is an effective and better tolerated alternative to infliximab, and would give patients and physicians a valuable therapeutic biologic option. |
| **Page 28 4.13** | The Committee noted that the economic model had not included health-related quality of life measured using a generic preference based measure, but had instead mapped a disease-specific measure (HAQ) to a generic measure (EQ-5D). The Committee noted that the manufacturer had chosen to do this because mapping HAQ to utilities had been used in previous NICE technology appraisals of treatments for rheumatoid arthritis in the absence of directly elicited EQ-5D data. The Committee noted that the manufacturer's mapping of HAQ scores to EQ-5D utility values resulted in the possibility of clinical scenarios where having rheumatoid arthritis would be worse than being dead. The Committee heard | Using a non-linear approach to map HAQ scores to EQ-5D utility values is one that has been accepted by previous Appraisal Committees and has become an accepted methodology. For example, in the appraisal leading to the publication of TA 130 it was noted (section 4.3.10 pg 27);<br><br>*"The Committee was aware of the limitations of using HAQ scores as a basis for estimating health-related quality of life in patients with RA. Namely that the HAQ is a measure of functional disability, which fails to capture the psychological and pain elements of quality of life associated with RA. In addition, the Committee noted that the HAQ scoring system may be an insensitive measure of small changes in health-related quality of life and may have a non-linear relationship to utility scores. The Committee noted that HAQ had been used as a basis for calculating utility across all the economic models, and while* |

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| | from the patient experts that it was possible that some people with rheumatoid arthritis may experience such severe disease. The Committee noted that estimates using a non-linear approach to mapping were more favourable to abatacept, and was aware of the manufacturer's sensitivity analysis that showed that using a linear utility mapping increased the ICER for abatacept plus methotrexate compared with conventional DMARDs plus methotrexate from £29,700 per QALY gained in the base case to £32,100 per QALY gained. | *noting its limitations, accepted that it was the best means of estimating utility for the purposes of the economic analysis given the available data".*<br><br>This approach of mapping HAQ to EQ-5D has also been described in the literature (Barton et al 2004);<br><br>*"However, it is possible that a better fit can be obtained from a non-linear relationship".*<br><br>BMS consider it perverse and unfair to compare abatacept against recommended products which have been approved utilising agreed methodologies, and then to refuse abatacept based on those same methodologies. BMS also consider it unjustified, in light of the above evidence, that an alternative methodology is suggested based solely on its effect on the resultant ICER, rather than using a scientific methodology based on its own merit in order to produce a valid ICER. |
| **Page 31 4.17** | The Committee considered the costs included in the economic model. The Committee heard the manufacturer acknowledge that it had used costs that included loss of productivity, and that this was outside the reference case defined by NICE. The Committee agreed that the costs proposed by the ERG were more appropriate. The Committee noted that including these costs increased the ERG's corrected base-case ICER from £29,700 to £29,900 per QALY gained. The Committee was also aware that costs of | BMS acknowledge that including productivity costs in the economic model was outside the reference case as defined by NICE. These costs were included in error. BMS therefore accept the additional analyses presented by the ERG utilising £1120 per HAQ unit. It is pertinent to note that with this amendment that abatacept remains cost effective against DMARDs.<br><br>It is very unlikely that abatacept, which is a human fusion molecule, could cause neutralising antibody production, which is the biological phenomenon which causes reduced efficacy in a biologic (which necessitates dose escalation). Indeed, data from |

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| | escalating the dose of abatacept were not included in the model. The Committee agreed that there was no evidence currently to suggest that people had a decreased response to abatacept over time; however, it considered that it was biologically plausible that this may occur in the future and in the long term, given the experience from other biological DMARDs. The Committee concluded that if people required increasing doses of abatacept over time, then this would increase the ICERs for abatacept plus methotrexate compared with conventional DMARDs. | the abatacept clinical studies show that such a phenomenon does not occur. In abatacept treated patients the immunogenicity rate is very low, and there has been no report showing that it translated into a loss of efficacy (Haggerty et al. 2006, Haggerty et al. 2007). Clinical trials experience has shown a sustained efficacy over 7 years (see Figure below) (Westhovens et al. 2009a) and a high retention rate of abatacept in the long-term extension of a number of trials (Westhovens et al. 2009, Kremer et al. 2009).<br><br>BMS therefore consider it would be inappropriate to include dose escalation of abatacept within the economic model. |
| **Page 32 4.19** | • omitting trials from the mixed treatment comparison<br><br>• modelling data from the HAQ score instead of DAS28 score | The mixed treatment comparison was produced in a robust and scientific manner. In addition the network of studies included in the MTC was validated using an advisory panel of 4 expert clinicians and a statistician in order to ensure that no studies were omitted.<br><br>Using the HAQ score for the purposes of economic modelling of RA has been used and accepted during numerous technology assessments for treatments for RA. Whilst the DAS 28 is more often used in clinical practice than the HAQ, and may give a better day to day clinical picture of the disease, the HAQ allows a better mapping to utilities. This has been well established, and used extensively for a number of years (Barton et al 2004). Importantly, there are two ways of calculating DAS score, (1) by using the ESR and (2) using CRP. In contrast, there is only one method by which to measure HAQ. This means that the DAS 28 scores very much |

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| | | depend on the chosen method of measurement, which is not always reported, and so will affect associated utilities in an inconsistent way. Indeed, the Technology Assessment Group (TAG) used this methodology in both TA130 (2007) and TA195 (2010). |
| | • the approach to mapping HAQ score to utilities | Using a non-linear approach to map HAQ scores to EQ-5D utility values is one that has been accepted by previous Appraisal Committees and has become an accepted methodology. In TA130 the committee noted, that while this methodology had its limitations, they accepted that it was the best means of estimating utility for the purposes of the economic analysis of RA given the available data. |
| | • the increase in mortality rate for each unit increase in HAQ score | The mortality rate for each unit increase in HAQ score was taken from the published literature which is the currently the only source available for this information. However different mortality rates were presented as sensitivity analysis. |
| | •the exclusion of costs or disutilities associated with adverse events from the model | The exclusion within the economic model of costs and the associated disutility related to adverse events is a conservative approach. A recent independent meta-analysis (Singh et al 2011) supported abatacept's favourable safety and tolerability profile, specifically in regard to serious infections. This is also supported by EPAR 2010 (Variation Assessment Report EMA/361627/2010). Therefore it is likely that the inclusion of adverse events in the model would see a reduction in the ICER in favour of abatacept. |

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| | • the inclusion of productivity costs | BMS acknowledge that including productivity costs in the economic model was outside the reference case as defined by NICE. These costs were included in error. BMS therefore accept the additional analyses presented by the ERG utilising £1120 per HAQ unit. It is pertinent to note that with this amendment at abatacept remains cost effective against DMARDs. |

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**Table 1. Details on doses used for the dose-adjusted analysis**

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| Etanercept | 25 mg SQ twice a week | 50 mg qweek |
| Infliximab | 3-5 mg/kg Q8 weeks; may increase to 10 mg/kg | 3 mg/kg q8weeks |
| Adalimumab | 40 mg SQ Q2 weeks | 40mg q2weeks |
| Golimumab | 50 mg SQ Q4 weeks | 50mg q4weeks |
| Certolizumab pegol | 400 mg SQ initially, then 200-mg Qother week or 400 mg monthly | 400 mg monthly |
| Anakinra | 100mg SQ Qday | 100 mg qday |
| Rituximab | 500 or 1000 mg -2 infusions, 2 weeks apart | 500-1000 mg 2wks apart |
| Abatacept | 500, 750 or 1000 mg Q4 weeks | 500-1000 mg Q4weeks |
| Tocilizumab | 4 mg/kg IV Q4 weeks; may increase to 8mg/kg Q8 weeks | 4 mg/kg q4weeks |

**(Singh et al. 2011)**