Abbott's response to the consultation on the West Midlands Health Technology Assessment Collaboration (WMHTAC) Technology Assessment Report: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

Executive Summary

Abbott welcomes the opportunity to comment on the assessment report for the appraisal of adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after failure of a TNF inhibitor for efficacy reasons.

Abbott considers it is necessary for patients to have access to a sequence of effective therapies to control the disease over their lifetime. Sequences of conventional DMARDs after failure of TNF inhibitors have no data to indicate that they will be effective in reducing disease progression in patients with moderate to severe disease. A sequence of therapy with multiple TNF inhibitors then followed by biologics with other mechanisms of action is necessary to avoid progressive functional impairment which is associated with a very low quality of life and high burden to patients, carers and the state.

The estimated incremental cost-effectiveness ratio for adalimumab versus conventional DMARDs is notably higher when using the BRAM reference case model than when using the model submitted by Abbott. It may be possible to reconcile the different estimates from the two models by taking account of two key factors. Firstly, the model submitted by Abbott explicitly stops patients who do not achieve a set level of response in the short term. Patients who are responders have a greater than average HAQ improvement in line with that observed in clinical trials. The BRAM model uses an alternative approach without an explicit categorisation of responders and non responders. In the BRAM, all patients remaining on therapy have an average HAQ improvement. Due to the different design of the models it is difficult to quantify what effect this has, however this is one reason why the cost per QALY estimates for biologics versus conventional DMARDs are higher in the BRAM compared to the model submitted by Abbott. The second reason why the model submitted by Abbott gives lower cost per QALY estimates than the BRAM model for biologics versus conventional DMARDs is likely due to the different assumptions for data inputs for effectiveness and time on drug for conventional DMARDs. In this respect Abbott is more pessimistic than the assessment group regarding the expected effectiveness of conventional DMARDs used at this line of therapy (post anti-TNF failure). Scenario analyses indicate that biologic options would be associated with cost per QALY estimates below £30,000 when a lower effectiveness of conventional DMARDs is assumed. It is important to consider the combined effect of shorter time on drug and lower HAQ multipliers with conventional DMARDs in the BRAM reference case analysis as both these sets of input parameters are likely to give an overestimate of QALY gain with conventional DMARDs. Furthermore, disparate sources for the input parameters have been used for the TNF inhibitors, other biologics and DMARDs without any adjustment for the different patient populations (early vs. late RA) or biases associated with the different type of data source e.g. clinical trials, retrospective data base analysis, prospective registry study.

Abbott considers that TNF inhibitors should be the preferred treatment option rather than rituximab after patients have failed a TNF inhibitor. There are a number of reasons supporting this sequence of treatments. Firstly, there is greater experience with TNF inhibitors in terms of patient-years of exposure in safety reporting. Secondly, studies of TNF inhibitors have not shown lower response rates among patients who were rheumatoid factor negative, whereas data suggest that rheumatoid factor negative patients receiving rituximab are less likely to respond, particularly when the effect on radiographic progression is assessed. Finally, the optimal interval for re-treatment with rituximab remains to be determined for TNF failure patients in UK clinical practice. The BRAM model applies an 8.7 month re-treatment interval for rituximab in the base case and notes that the cost effectiveness of rituximab varies markedly based on the time to re-treatment. However, this analysis varied only the cost for rituximab and assumed that the effectiveness of rituximab is the same when given every 6 months or every 8.7 months. The cost and effectiveness of rituximab should not be considered to be independently associated with the re-treatment interval. That is to say, rituximab re-treatment should occur more frequently than the

currently applied mean of 8.7 months in order to maintain disease control. This is because data are available which indicate that treatment every 9 months could lead to less tight disease control (data suggest dosing every 25 weeks for disease control).

At 6-month re-treatment intervals for rituximab, both the BRAM model and the Abbott model show that the cost-effectiveness of rituximab is similar to the TNF inhibitors. Alternatively, if an 8.7 month re-treatment interval is assumed, it is difficult to model the cost-effectiveness of rituximab, as the evidence used for clinical effectiveness is based on the 24-week response rates and does not account for the observed loss of efficacy over time. The potential for longer term functional impairment needs to be given due weight in the interpretation of the cost effectiveness analyses of TNF inhibitors versus rituximab based on 8.7-month re-treatment intervals.

1. Cost effectiveness of TNF inhibitors versus conventional DMARDs

The estimated incremental cost-effectiveness ratio (ICER) for adalimumab versus conventional DMARDs is notably higher when using the BRAM reference case model than when using the model submitted by Abbott. Despite having different model structures and applying a number of different data inputs Abbott considers that it is possible to reconcile the different estimates from the two models by taking account of two key factors.

Firstly, the model submitted by Abbott explicitly stops patients who do not achieve a set level of response in the short term. Patients who are responders have a greater than average HAQ improvement in line with that observed in clinical trials. The BRAM model uses an alternative approach without an explicit categorisation of responders and non responders. In the BRAM all patients remaining on therapy have an average HAQ improvement. Due to the different design of the models it is difficult to quantify what effect this has on the BRAM. A sensitivity analysis run on the model submitted by Abbott shows that not withdrawing non-responders increases the ICER by more than 50%.Therefore, this is one reason why the cost per QALY estimates for biologics versus conventional DMARDs are higher in the BRAM compared to the model submitted by Abbott. Since withdrawal in the BRAM is not linked to response status, patients who are responding to treatment are less likely to stay on treatment than in the Abbott model while non-responders are more likely to continue on treatment. The impact of this disconnect between response and withdrawal rates reduces the potential QALYs attainable, whilst increasing costs, with a bias against more effective treatments.

The second reason why the model submitted by Abbott gives lower cost per QALY estimates than the BRAM model for biologics versus conventional DMARDs is likely due to the different assumptions for data inputs for effectiveness and time on drug for conventional DMARDs. In this respect Abbott is more pessimistic than the assessment group regarding the expected effectiveness of conventional DMARDs used at this line of therapy (post anti-TNF failures). In an effort to synthesise evidence and reduce the effect of different populations and baseline variables in different trials, the model submitted by Abbott relies on results from a mixed treatment comparison (MTC) of ACR responses that synthesised evidence from all available clinical trials and calculated effectiveness of biologics and DMARDs in the anti-TNF failure population. These results are translated into a HAQ response by using ACR specific HAQ reductions. The results for the methotrexate arm used for conventional DMARDs show a lower effectiveness post anti-TNF failure than the parameters in the Assessment Group's model.

Abbott considers that there is little evidence to support DMARD effectiveness in these patients and that therefore the current BRAM data inputs for conventional DMARD effectiveness should be revised downwards. Scenario analyses indicate that biologic options would be associated with cost per QALY estimates below £30,000 when a lower effectiveness of conventional DMARDs is assumed. The magnitude of reduced effectiveness is difficult to calculate due to an absence of appropriate data for conventional DMARDs, and further consideration by rheumatologists may therefore be warranted to ensure that data inputs applied in the model are in accordance with clinical experience in this patient population. In this respect Abbott considers that the assumption that leflunomide is marginally more effective in terms of short term HAQ improvement than etanercept, infliximab or rituximab would not be supported by the majority of rheumatologists with experience of treating patients who have failed a TNF inhibitor for efficacy reasons.

1.1 Application of early RA trial data to estimate the effectiveness of conventional DMARDs

As has been extensively discussed in previous correspondence on this issue, there is a paucity of evidence available for the effectiveness of conventional DMARDs in a TNF inhibitor failure population. This data gap is not only wide for patients failing a TNF inhibitor, it also exists for patients failing two prior DMARDs as no randomised controlled trials have considered the effectiveness of conventional DMARDs after failure of two DMARDs in patients with established/ late RA with many years of disease duration. One of the consequences of the lack of data on the effectiveness of conventional DMARDs in later lines of therapy is that it is difficult to precisely quantify the cost effectiveness of biologic therapies versus conventional DMARDs. The outcome of this uncertainty could be the restriction of biologic therapies

leading to use of conventional DMARDs in anti-TNF failure populations with minimal effect. As one option, given the absence of appropriate clinical trial data for conventional DMARDs, it may be instructive to assess their effectiveness using observational data. The limited observational data from the BROSG and BSRBR studies indicate that sequential use of conventional DMARDs after methotrexate failure in late RA does not significantly improve HAQ scores in either the short term or long term. Whereas, there is increasing body of evidence that indicate that TNF inhibitors are associated with clinically significant improvements in physical function in patients with advanced disease who have failed multiple DMARD therapy. Another important point to note is that TNF inhibitors have been shown to significantly reduce radiographic progression compared to conventional DMARDs. Evidence is available that reducing radiographic progression leads to long term maintenance of functional ability and ability to remain in employment[1]. It is therefore important to consider the impact of a treatment on both signs and symptoms and radiographic progression when assessing the effect on long term functional impairment due to RA.

Although the populations in the above studies do not adequately reflect the anti-TNF failure population, given that sequences of conventional DMARDs have not been able to reduce HAQ scores in studies of late RA it is highly unlikely that this would be possible in the more severe anti-TNF failure population (who have failed two or more DMARDs prior to failing their first TNF inhibitor).

Given the uncertainty regarding the effectiveness of conventional DMARDs for use in patients failing a TNF inhibitor for efficacy reasons, it is important to consider a range of estimates for their effectiveness in the cost effectiveness modelling. The reference case BRAM model attempts to adjust for the reduced effectiveness of conventional DMARDs in the anti-TNF failure population by arbitrarily assuming that their effectiveness would be 50% of that observed as a first line therapy in patients with early RA in clinical trials, as outlined in Table 75 of the assessment report:

Table 1.1.1: HAQ multipliers applied in the BRAM model (the higher the mean the more effective the treatment is in reducing HAQ)

Table 75 Beta distributions for HAQ multipliers (point estimates)

Treatment	*A*	*b*	Mean	Source
ADA	0.32	0.92	0.26	Bombardieri 2007[93,94]
ETN	0.21	0.75	0.22	Bingham 2009[102]
IFX	0.21	0.75	0.22	Assume same as ETN
RTX	0.20	0.75	0.21	REFLEX[122-124]
ABT	0.33	0.85	0.28	ATTAIN[125-130]
LEF	0.285	0.935	0.23	Effectiveness halved from values used in previous report[153]
GST	0.225	0.925	0.20	
CyA	0.065	0.325	0.17	
AZA	0.10	0.90	0.10	

For probabilistic sensitivity analysis, the values a and b are drawn from Normal distributions with standard deviation 0.1 times the point estimate (see text).

However, even with this adjustment, leflunomide is considered to be more effective than etanercept, infliximab or rituximab in reducing the HAQ score of TNF failure patients in the short term. Given the absence of data the appropriateness of this assumption requires further validation by clinical experts.

As an alternative to the use of observational data, the cost-effectiveness analysis included in Abbott's submission used the results of a meta-regression/ MTC as a measure of effectiveness. The metaregression/ MTC was uniquely built to take into account the effect of applying treatments after failure of a first TNF inhibitor. It synthesised evidence from a large number of trials and estimates ACR

responses for TNF failure patients on any treatment. Combining the ACR response rates from this MTC for adalimumab and conventional DMARDs with the HAQ reductions observed for each level of ACR response in the adalimumab DE019 RA study provides alternative estimates for the HAQ multipliers. As discussed in the Abbott submission, the average starting HAQ score in DE019 was 1.5 which is lower than would be observed in patients who have failed TNF inhibitor therapy historically in the UK. Subgroup analysis of DE019 showed that HAQ improvements were lower in patients with a starting HAQ >2 than those achieved by the entire DE019 study population. Although patient numbers are small, in order to be conservative, this analysis was conducted for the subgroup of patients with a starting HAQ >2 only. The resulting HAQ multipliers are shown in Table 1.1.2 below.

Table 1.1.2: HAQ multipliers based on Mixed Treatment Comparison*

Response rate	**Proportion of patients in each response category at 6 months - Results from MTC**	**ACR specific relative HAQ reductions over 6 months**	**Resulting HAQ at 6 months**	**Reduction in HAQ**
Adalimumab				
Non-responder	36%	-17.3%	1.65	
ACR 20-50	24.1%	-28.9%	1.42	
ACR 50-70	19.6%	-37.3%	1.25	
ACR 70+	20.5%	-76.5%	0.47	
Weighted Average			1.2765	**36.2%**
DMARDs				
Non-responder	74.7%	-8.4%	1.83	
ACR 20-50	14.9%	-22.3%	1.55	
ACR 50-70	6.3%	-66.9%	0.66	
ACR 70+	4.1%	-76.5%**	0.47	
Weighted Average			1.6611	**16.9%**

*Assume starting HAQ=2. ** assumed the same as for adalimumab, as there were no ACR70 responders in the HAQ>2 subgroup within the MTX + placebo arm.

As can be seen in Table 1.1.2, using this approach to estimate the HAQ multipliers results in a larger change in HAQ score for adalimumab patients when compared to the values used in the BRAM model (36.2% versus 26%), while the DMARD multiplier is similar to that used for ciclosporin (16.9% versus 17%), and lower than that applied for leflunomide and gold.

Applying these HAQ multipliers reduces the ICER of adalimumab versus conventional DMARDs significantly to £25,900 per QALY.

It is clear from the Assessment Report that the BRAM model is sensitive to the HAQ multipliers used for the different treatment options, yet scenario analyses have not been performed to investigate different HAQ multipliers and their subsequent impact on the cost-effectiveness estimates for the biologics vs. conventional DMARDs. Given the HAQ multipliers are a notable driver in the cost-effectiveness estimates, Abbott has conducted a number of additional scenario analyses using the BRAM model to assess the impact of the uncertainty regarding the effectiveness of conventional DMARDs on the ICERs of different biologic options versus conventional DMARDs. These are outlined in Table 1.1.3.

Table 1.1.3 Scenario analyses using the BRAM, assuming lower effectiveness of conventional DMARDs and that patients remain on conventional DMARDs for no longer than TNF inhibitors on average

Scenario	ADA – DMARDs	ETN – DMARDs	IFX - DMARDs	RTX - DMARDs	ABT - DMARDs
Reference	£34,300	£38,800	£36,200	£21,200	£38,600
HAQ multipliers set at ¼ of early RA efficacy for conventional DMARDs.	£28,000	£31,200	£28,600	£16,300	£31,900
HAQ multipliers set equal to azathioprine for all conventional DMARDs	£28,800	£31,700	£29,500	£16,800	£32,600
HAQ multipliers for all conventional DMARDs as per base case and Weibull parameters for long term drug survival set equal to TNF inhibitors	£32,100	£36,000	£33,200	£19,700	£36,100
HAQ multipliers set equal to azathioprine and Weibull parameters for long term drug survival for all conventional DMARDs set equal to TNF inhibitors	£27,900	£31,200	£28,800	£16,500	£31,800
HAQ multipliers set at ¼ of early RA efficacy for conventional DMARDs. Weibull parameters for long term drug survival for all conventional DMARDs set equal to TNF inhibitors	£27,600	£30,500	£28,300	£16,100	£31,400

2. Long term effectiveness and time on drug for the different drugs considered

There is uncertainty regarding how to model the long term discontinuation rates of rituximab, abatacept or conventional DMARDs compared to TNF inhibitors, as there are no data available from the BSR Biologics Register to indicate the comparative drug survival in UK clinical practice for this patient population. The BRAM model estimates Weibull survival curves for the TNF inhibitors based on the BSRBR, for rituximab discontinuation rates are based on a long term extension of the REFLEX clinical trial, for abatacept they are based on data included in the manufacturer's submission, and for conventional DMARDs discontinuation rates are based on drug survival for all RA patients treated between 1987 and 2002 from the General Practice Research Database, as shown in Table 77 of the Assessment Report (Table 2.1 below):

Table 2.1: Weibull parameters for long term drug survival in the BRAM model

Table 77 Times to quitting treatments

Treatment	*a*	95%CI	*b* (years)	95%CI	Mean (years)	Source
TNF inhibitors	0.701	(0.634,0.768)	3.211	(3.022,3.412)	4.06	BSRBR submission[121]
RTX	0.474	(0.403,0.545)	5.1	(3.742,6.951)	11.31	REFLEX long-term extension[137]
ABT	0.81	(0.734,0.886)	5.49	(5.166,5.834)	6.17	BMS submission[158]
LEF	1	(0.905,1.095)	5.98	(5.627,6.355)	5.98	GRPD database[159]
GST	0.48	(0.434,0.526)	1.81	(1.703,1.923)	3.91	
CyA	0.5	(0.452,0.548)	4.35	(4.094,4.623)	8.70	
AZA	0.39	(0.353,0.427)	4.35	(4.094,4.623)	15.53	

Normal distributions used for parameter a; lognormal for parameter b. Standard errors for TNF inhibitors and RTX estimated from data. For other treatments, the same proportional variability as for TNF inhibitors has been assumed. Mean team on treatment based on the point estimate of the parameters.

These data indicate that patients would remain on conventional DMARDs on average for the longest time period, followed by rituximab, then by the TNF inhibitors. However, the rates come from different types of data sources (retrospective database analysis, clinical trials, and prospective registry study) and also from different time periods, which makes these data points very difficult to compare without some form of adjustment.

Given that the data in Table 2.1 reflect time on DMARDs for all RA patients without regard to line of therapy or disease severity, it is highly likely that these data overestimate drug survival on conventional DMARDs for anti-TNF failure patients. Data are available from an observational study by Aletaha *et al.* which indicate that discontinuation rates for conventional DMARDs were significantly higher for patients who had failed previous DMARD therapy[2]. The impact of these drug survival data on the cost effectiveness of biologic therapies versus conventional DMARDs should be analysed in further sensitivity analyses.

Similarly, there is little evidence on time on treatment in a UK clinical setting for rituximab. However, extrapolation from a clinical trial may be overly optimistic about treatment duration, particularly when this is coupled with a model structure that does not allow early discontinuation (or in other words loss of efficacy) with rituximab within each cycle. It should be noted for the comparison of TNF inhibitors versus rituximab that patients who remained in the long term extension to the REFLEX RCT were more likely to be good responders and therefore provide an inappropriate comparison with all TNF inhibitor patients in the observational BSRBR study. Furthermore, an open-label extension study where the cost of the drug is paid for by the manufacturer potentially introduces a significant bias towards continuation on drug and is therefore not comparable to clinical practice in the UK, where there are strict criteria for drug continuation. In addition, the RELFEX study was a multinational study and therefore the participants included in the trial will not necessarily represent the access criteria for a biologic in the UK, which are subsequently captured by the BSRBR. In this respect, it is appropriate to consider shorter drug survival for rituximab in the economic modelling, as it is unlikely that patients would on average remain on rituximab for 11.31 years compared to 4.06 years on a TNF inhibitor.

It is important to consider the combined effect of shorter time on drug and lower HAQ multipliers with conventional DMARDs in the reference case analysis as both these sets of input parameters are likely to give an overestimate of the QALY gain with conventional DMARDs.

3. Issues regarding the clinical effectiveness, cost effectiveness and safety of treatment with rituximab

3.1 Optimal re-treatment dosing with rituximab

The BRAM model applies an 8.7 month re-treatment interval for rituximab in the base case and notes that the cost-effectiveness of rituximab varies markedly based on the time to re-treatment. At 6-month re-treatment intervals for rituximab, both the BRAM model and the Abbott model show that the cost-effectiveness of rituximab is similar to the TNF inhibitors. However, the analysis only varied the cost for rituximab by differing re-treatment intervals and assumed that the effectiveness of rituximab was the same when given every 6 months or every 8.7 months. The modelling is based on the 6-month response rates observed in the rituximab REFLEX trial and not the response rates at 8.7 months. In the NICE guidance for TNF inhibitors in TA130, for continued treatment of TNFs the maintenance of DAS28 reduction of 1.2 is required, but such a requirement does not appear to be in place for rituximab (TA126). Not including response based discontinuation generates greater QALYs for rituximab without increasing costs beyond the 8.7 monthly cycle, which biases the results against the anti-TNFs. Abbott considers that the mean re-treatment interval for rituximab would be less than 8.7 months in UK clinical practice when patients would be re-treated to maintain adequate DAS28 response. Alternatively, if an 8.7-month mean re-treatment interval is applied then this dosing regimen should be associated with commensurately lower QALY gains for rituximab, as patients losing response would suffer a reduction in their quality of life until re-treated. It is unknown whether this would have any long term effect on disease progression as it will be necessary to analyse long term follow up data from registries to test the relationship between fluctuating disease activity and long term functional impairment.

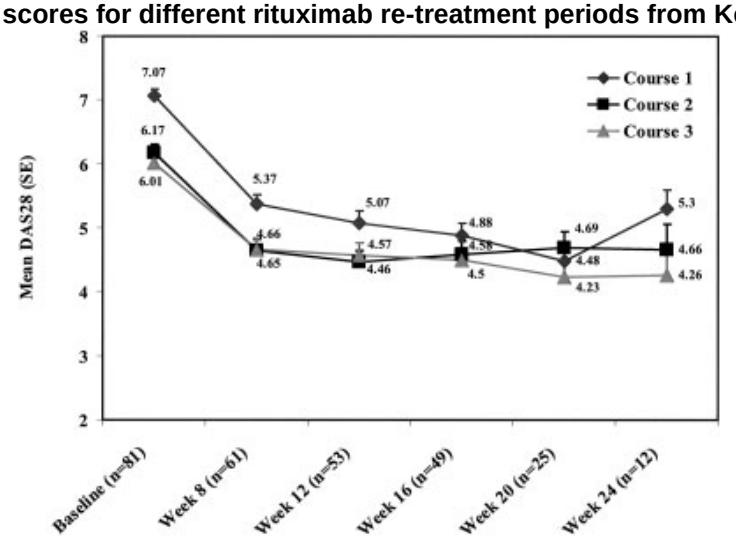
In the BRAM model the annual cost of rituximab is given as £6,204. This is based on a mean re-treatment period of 8.7 months, but uses the 24 week HAQ improvements in the REFLEX study. Of note, the timing of re-treatment with rituximab was based on tender and swollen joint counts in clinical studies in anti-TNF failure patients and not dependent on the need to maintain a pre-defined change in DAS28[3]. The current EMEA marketing authorisation for rituximab does not give any guidance as to the time period between treatments for rheumatoid arthritis, simply the minimum time between re-treatment (16 weeks). However, in June 2009 the manufacturer of rituximab filed a variation to the EMEA seeking approval for first line biologic use of rituximab in RA patients who have failed conventional DMARD therapy. The data supporting this variation are based on the MIRROR and SERENE trials which all specified re-treatment with rituximab starting at 24 weeks for patients with a DAS28 score ≥ 2.6 . Given that the patient population for these trials have not failed a prior TNF inhibitor, then this suggests that re-treatment with rituximab in patients who have failed a TNF inhibitor is likely to be at least every 24 weeks, to ensure maintenance of response.

Post-hoc analyses of re-treatment with rituximab in anti-TNF naïve patients indicate that re-treatment to maintain a DAS28 score ≤ 2.6 gives better disease control than re-treatment without regard to specific disease activity levels[4]. Furthermore, when the re-treatment protocol was to maintain a DAS28≤ 2.6 , the median time to re-treat was a 25-week interval. Patients receiving rituximab re-treatment without regard to keeping DAS28 score ≤ 2.6 had high DAS scores at time of re-treatment (DAS28 scores were 5.9 to 6.2 at time of re-treatment depending on which course of re-treatment was assessed, i.e. close to baseline DAS28 levels). This loss of response would have led to withdrawal of therapy if a TNF inhibitor were being used, in line with the guidance given in TA130. The worsening of DAS28 score was also associated with higher levels of withdrawals due to disease flares. The impact of this lower level of control will need to be assessed in long term follow up of radiographic progression and functional impairment in observational studies.

Keystone *et al.* have also assessed the DAS28 score of patients prior to re-treatment with rituximab. In this open-label extension study, patients were enrolled from three rituximab phase II and III trials in patients previously treated with TNF inhibitors. They were eligible for repeated courses of rituximab based on certain criteria: a <20% reduction in tender and swollen joint count from baseline, with associated active disease defined as >8 tender and swollen joints present. Clinical efficacy, as measured by DAS28,

was analysed at 24 weeks (see Figure 3.1.1) but the median time between courses of re-treatment was 38 weeks (course 1 to 2) and 42 weeks (course 2 to 3). In the period between 24 weeks and re-treatment with the next course, the DAS28 demonstrates a poor clinical response with return to near baseline values (DAS28 of 6.17 before initiating the second course of rituximab).

Figure 3.1.1: DAS28 scores for different rituximab re-treatment periods from Keystone *et al.*



This has implications for optimal disease management and the cost-effectiveness estimates for rituximab. The loss of efficacy between 24 and 38 weeks would suggest more frequent dosing (i.e. every 16-24 weeks) is required to maintain disease control and keep the DAS28 improvement greater than the 1.2 reduction required for re-treatment under NICE guidelines for adalimumab, etanercept and infliximab.

From the Keystone data it would suggest that patients can either be re-treated at ≥6 month intervals when they will have lost efficacy and returned to near baseline disease activity, or at more frequent intervals which maintains control but has obvious higher cost implications. By 6-9 months, neither option fulfils current NICE guidance for TNF inhibitors with respect to a DAS28 reduction ≥ 1.2 or re-treatment at intervals >6 months. The mean DAS28 for the Keystone study population just prior to course 1 was 7.01 and just prior to course 2 re-treatment was 6.17, or a reduction of 0.84, showing that patients are not being maintained with a DAS28 improvement ≥ 1.2 . Evidence is becoming increasingly available that aggressive, rapid and maintained disease control is important to prevent disease progression, disability and reduced quality of life[5]. Therefore, it is a concern that were an 8.7 month re-treatment interval be proposed, the significant disease activity between months 6-9 may have detrimental effects on disease progression and subsequent disability.

The effect of the two assumptions: 8.7-monthly re-treatment and no HAQ progression throughout the whole treatment course on the cost-effectiveness of rituximab, are both significant in the BRAM model. In a scenario analysis, with an 8.7 month re-treatment period, with an annual HAQ progression of 0.02 per annum (or mean time to a 0.125 change in HAQ of 6.2 years), the ICER for rituximab against traditional DMARDs increases to £33,200. However, this scenario does not capture the cyclical nature of efficacy loss evidenced by Keystone *et al.* (see above). At the same time the fact that such a small HAQ progression reduces the QALYs gained by rituximab to 2.77 highlights the importance of the assumption in the base case that efficacy remains constant throughout the complete 9 month cycle. A similar scenario is presented for all treatments in the Assessment Report (0.03 HAQ progression per annum); however, it can be argued that the reference case should treat rituximab differently from other biologics, due to the nature of the dosing and potential for loss of disease control when the re-treatment interval is greater than 6 months.

A rituximab-specific univariate change in HAQ progression has a major impact on the adalimumab versus rituximab comparison, bringing the ICER to around £40,300/QALY with a 0.02 annual HAQ progression and £15,700/QALY with a 0.03 annual HAQ progression.

The results of the rituximab dosing scenario analyses presented in the Assessment Report are somewhat counterintuitive in terms of QALYs gained. The longer re-treatment periods (8.7 and 11.6 months) are associated with lower costs AND higher QALYs than the 6-month retreatment. Based on the clinical evidence presented above, less frequent re-treatment should be associated with worse efficacy results due to less tight disease control towards the end of the treatment course.

Abbott considers that the optimal interval for re-treatment with rituximab and associated outcomes remain to be determined for UK clinical practice but the cost and effectiveness of rituximab should not be considered to be independently associated with the re-treatment interval. The modelling of rituximab costs should not be independent of treatment effect, that is to say, the modelling of QALY gains achievable with rituximab should take account of lower quality of life improvements when patients have lost response, as defined by maintenance of a 1.2 point DAS28 improvement. Either rituximab re-treatment should occur more frequently than the currently applied mean of 8.7 months (i.e. every 16-24 weeks[3,6,]), or the loss of efficacy observed prior to re-treatment at 8.7 months and potential for longer term functional impairment needs to be given due weight in the interpretation of the cost effectiveness analyses. Abbott considers that the cost-effectiveness of rituximab is overestimated by simultaneously applying costs based on an 8.7-month re-treatment interval with effectiveness based on the initial 6-month HAQ improvements.

3.2 Safety of treatment with rituximab in RA patients

The safety of rituximab needs to be given due consideration in this appraisal considering the increased risk of Progressive Multifocal Leukoencephaolopathy (PML) in RA patients receiving rituximab detailed in the SmPC[7]. In September 2009, Genentech and the FDA notified healthcare professionals about a case of PML in a patient receiving treatment with rituximab for rheumatoid arthritis (the patient had not previously been treated with methotrexate or a TNF inhibitor) [8]. This represents the third fatal case of PML in an RA patient receiving rituximab which now has a black box safety warning regarding the infectious demyelinating condition[9,10]. Interestingly, rituximab treatment has also been associated with the development of PML in a number of other conditions: in a recent publication 52 patients with lymphoid malignancies, 2 patients with SLE, 1 patient with rheumatoid arthritis, 1 patient with idiopathic autoimmune pancytopenia, and 1 patient with immune thrombocytopenia purpura all developed PML after rituximab treatment[11]. The case fatality rate was 90% for these patients. As of July 29, 2008, there were 76 reports in the manufacturer's global safety database of confirmed or suspected PML in patients receiving rituximab in any indication[12]. This further highlights the need for increased awareness and reporting of rituximab-associated PML cases in order to improve our understanding of the risk factors, natural course, and alternative therapeutic approaches. Overall, the reported incidence of PML in patients with RA receiving rituximab is rare (3 reports in approximately 100,000 RA patients on rituximab). However, the information to date suggests that patients with RA who are treated with rituximab have an increased risk of PML.

Overall, the level of rituximab exposure (patient-years) is low in rheumatoid arthritis compared to the TNF inhibitor class and it is important to bear this in mind when analysing the clinical efficacy and safety data. As of September 2008, pooled data from the rituximab global clinical trial programme showed a total of 3,095 patients had been treated with rituximab for rheumatoid arthritis providing 7,198 patient years of treatment[13]. However, only 750 patients (24%) remained on treatment for greater than 3 years with 2,365, 1,581, 1,038 and 497 patients receiving ≥2, ≥3, ≥4 and ≥5 courses respectively. Taken together, the long-term impact of sustained CD20+ cells depletion on relevant safety concerns and immune memory functions remains unanswered for this patient population.

Furthermore, there is limited experience regarding the safety of giving TNF inhibitors after rituximab therapy[14]. Safety data are currently available for only 178 patients who have received a TNF inhibitor after rituximab, with a median follow up of 11 months (191.72 patient-years). Given that in REFLEX, treatment

with rituximab was associated with a rapid and complete depletion of CD19 positive peripheral B cells, (with some recovery of cell counts beginning between weeks 16 and 20) with a non-existent median CD19+ve B cell count at week 24, poor responders to rituximab will have severely limited treatment options as the safety of further biologic therapy in patients with low or no circulating peripheral B cells is largely unknown. Preliminary data from patients who withdrew from rituximab therapy during rituximab clinical trials and then started treatment with either conventional DMARDs and/or TNF inhibitor therapies have been reported (n=153)[15] and show a near doubling of the serious infection rate in those that switched to TNF inhibitors. However, the overlapping 95% confidence intervals do not permit inference of a significant difference between rates before and after TNF inhibitor therapy in this analysis.

Given these issues around treatment options for patients who do not respond to rituximab, and the duration of disease for RA patients, it makes sense clinically to exhaust treatment options at each step of the treatment pathway before moving on to the next level. Current practice suggests that at least two DMARDs are tried before initiation of anti-TNF therapy, and the NICE clinical guidelines support this by suggesting patients diagnosed with RA are given combination DMARDs within 3 months of diagnosis. The next step after DMARD failures would be anti-TNF therapy. If a patient loses response to more than one member in this class, they should then move on to rituximab, as once rituximab has been given, evidence suggests that patients cannot go back.

3.3 Effectiveness of TNF inhibitors and rituximab for Rheumatoid Factor negative patients

In contrast to the data available for rituximab, studies of TNF inhibitors have not shown lower response rates among patients who were Rheumatoid Factor negative (RF-). Data outlined in this section include studies of TNF inhibitors and rituximab for TNF naïve patients as the sample sizes of these studies are greater than anti-TNF failure studies and, therefore, include a greater number of rheumatoid factor negative patients.

Data presented by Hyrich *et al.* from the BSRBR indicate that TNF inhibitors have shown comparable efficacy in both RF+ and RF- patients[16]. Analysis of the DE019 study of adalimumab (Keystone *et al*[17]) versus placebo found that RF- patients had similar levels of ACR response as RF+ patients (Table 3.3.1). The impact of adalimumab on radiographic progression in DE019 (as assessed using the Total Sharp Score) was also not affected by whether patients were RF+ or RF-.

Table 3.3.1: Percentage of patients achieving ACR 20 response at week 24 in the DE019 study of adalimumab by RF status

	ACR 20 response rate at week 24 (primary endpoint)		Relative Risk
	Adalimumab 40mg every other week	Placebo	
Rheumatoid Factor positive	66%	30%	2.2
Rheumatoid Factor negative	67%	33%	2.0

As can be seen in Table 3.3.2, this finding is also supported by data from the large observational ReACT study.

Table 3.3.2: Percentage of patients achieving ACR 20/50/70 response at week 12 in the ReACT study of adalimumab by RF status (as observed)

Response type	RF + n=4811	RF - n=1788
ACR 20	69.7%	66.7%
ACR 50	41.3%	37.0%
ACR 70	18.4%	17.9%
EULAR moderate or good response	83.3%	81.3%
EULAR good response	31.9%	36.6%

Sub-group analysis of data from the ReACT study indicates that the pattern of a similar response rate observed between RF+ and RF- patients treated with TNF inhibitors is consistent for patients who are both anti-TNF naïve and for those who have previously received another anti-TNF.

Table 3.3.3 Percentage of anti-TNF naïve patients achieving ACR 20/50/70 response at week 12 in the ReACT study of adalimumab by RF status (as observed)

Response type	RF + n=4160	RF - n= 1541
ACR 20	70.9%	68.3%
ACR 50	42.4%	38.1%
ACR 70	19.3%	18.6%
EULAR moderate or good response	84.4%	82.2%
EULAR good response	33.3%	38.5%

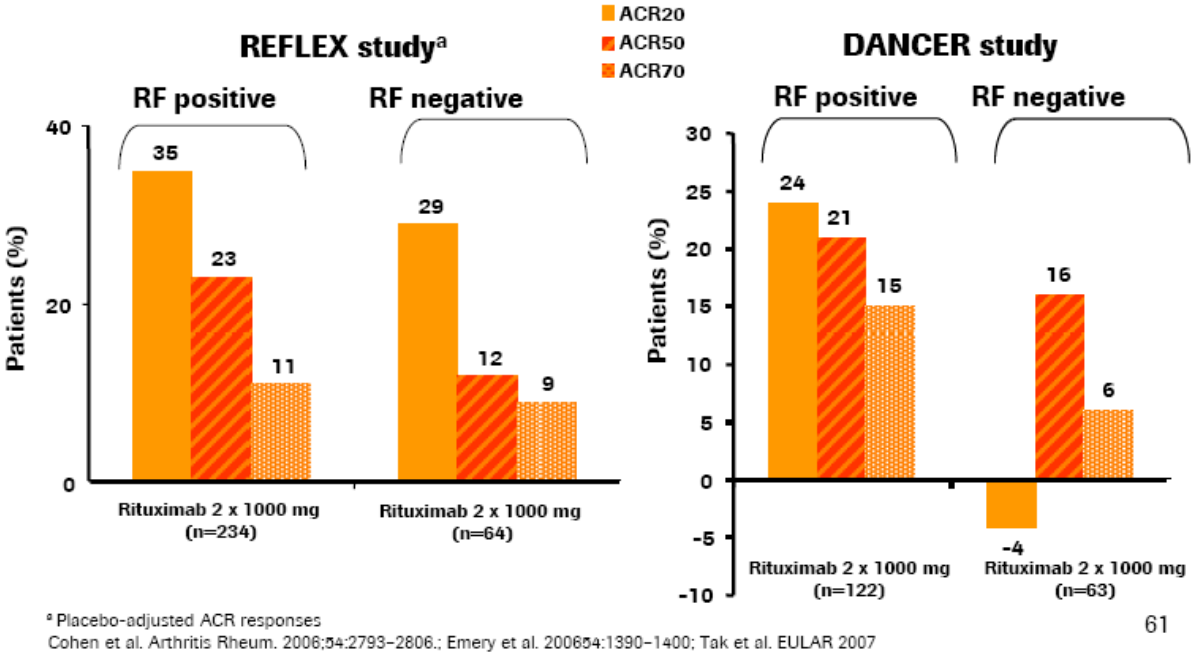
Table 3.3.4 Percentage of previous anti-TNF failure patients achieving ACR 20/50/70 response at week 12 in the ReACT study of adalimumab by RF status (as observed)

Response type	RF + n=651	RF - n= 247
ACR 20	61.6%	55.9%
ACR 50	34.1%	30.1%
ACR 70	12.6%	12.9%
EULAR moderate or good response	76.5%	75.6%
EULAR good response	22.6%	23.9%

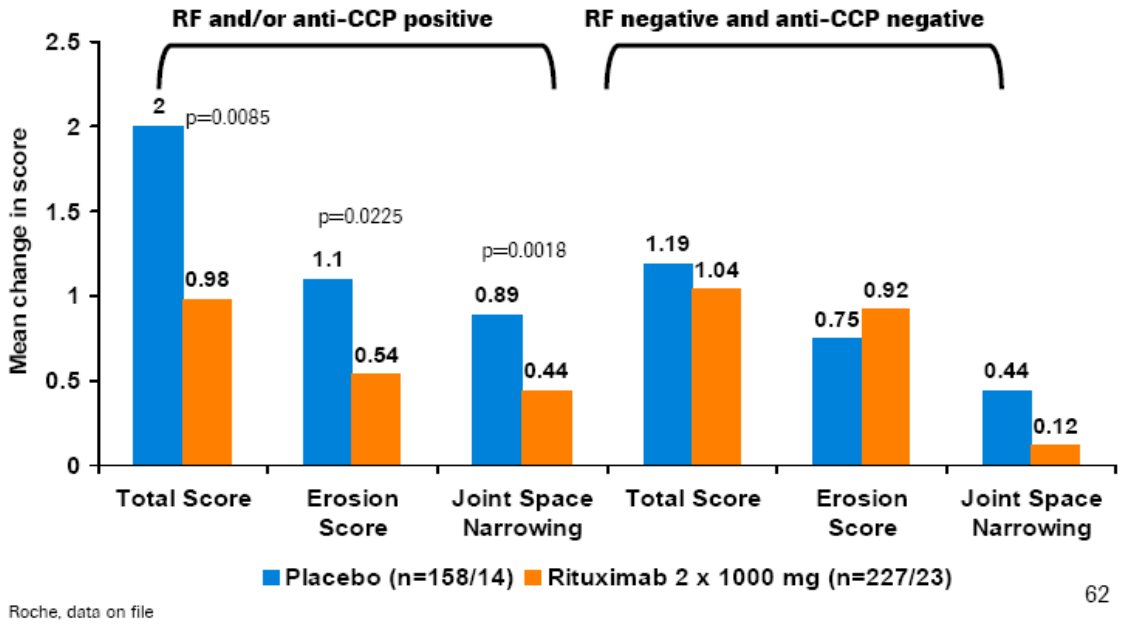
Both the ReACT and BSRBR studies have very large samples of rheumatoid factor negative patients to confirm the hypothesis that patients receiving TNF inhibitors do not have lower response rates when they are RF negative.

Conversely, limited published data from clinical trials indicate that RF-negative patients do not respond as well to rituximab as RF+ patients. Figure 3.3.1 shows that RF- patients in the DANCER and REFLEX studies had lower ACR response rates than RF+ patients[18].

Figure 3.3.1: Placebo adjusted percentage of patients achieving ACR20/50/70 in the REFLEX and DANCER studies of rituximab.



Furthermore, analysis of the REFLEX clinical trial data has shown that patients seronegative for Rheumatoid Factor (RF-) and/or anti-CCP negative have no significant difference in radiographic progression at week 56 when compared with placebo (Figure 3.3.2)[19] This is in contrast to the data from DE019 which found that impact of adalimumab on radiographic progression in DE019 was also not affected by whether patients were RF+ or RF-.



As noted by the Assessment Group, an unusually high number of RF- placebo patients in the DANCER study had an ACR20 response, and the numbers of RF- negative patients were low. Given this uncertainty, it is worthwhile considering other studies of rituximab in RA patients. In the phase III studies MIRROR and SERENE, patients seropositive for Rheumatoid Factor (RF+) and / or anti-CCP, showed enhanced clinical responses to rituximab when compared to seronegative patients[20]. A pooled cohort of patients was analysed which included patients with active RA where RTX was added to existing methotrexate. Rituximab was given by IV infusion on days 1 and 15 at doses of 2 x 500mg or 2 x 1000mg and from Week 24 further courses of RTX were permitted according to individual study criteria. Patients positive for either or both RF / anti-CCP were compared with those who were seronegative for both. A total of 670 patients were included (554 [82.6%] seropositive, 116 [17.4%] seronegative). Despite similar baseline demographics and characteristics, seropositivity was associated with a significantly greater proportion of patients achieving ACR20/50/70, EULAR responses and DAS28 remission versus seronegative patients. Seropositive patients were 2-3 times more likely to achieve a clinical response at week 48 versus seronegative patients - odds ratios (95% CI) for seropositive pts achieving ACR 20, 50 and 70 were 2.23 (1.38–3.58), 2.72 (1.58–4.70) and 3.3 (1.40–7.82) respectively, versus seronegative patients.

These data indicate that patients who were RF negative and anti-CCP negative had lower response rates. It would be interesting to know whether patients who were RF negative alone had lower response rates, as these studies may have a sufficiently large sample size when pooled to confirm this hypothesis.

Data on response by RF status are available in an observational cohort of patients on rituximab from European registries (n=1,372)[21]. These data indicate that 14.4% of patients receiving rituximab were RF-negative. These patients were less likely to be EULAR responders in a logistic regression analysis, although it should be noted that this difference was not statistically significant (Odds Ratio for RF+ status 1.5, 95% CI 0.96-2.0). These data indicate that a smaller proportion of patients receiving rituximab in clinical practice are RF- compared to patients receiving TNF inhibitors. Hyrich et al. reported 28% of TNF inhibitor patients as RF- in the BSRBR.

4. Comments on further aspects of the BRAM model

4.1 Consideration of the need for re-treatment and loss of efficacy with treatment

The BRAM assumes that HAQ scores remain constant while on any biologic treatment and that patients cannot withdraw from treatment until the time of the next dose. This assumption is reasonable for those treatments such as adalimumab which are administered regularly and a response is maintained over time. However, as discussed in section 3.1, a course of rituximab treatment is given at baseline but there are no strict guidelines as to how often patients should be re-treated. However, evidence does indicate that patients lose response over time, and those patients with a longer time between treatments experience deterioration in their disease control. The assumption that rituximab patients do not experience any deterioration in their HAQ score therefore overestimates the QALYs in the rituximab arm, particularly in those analyses which assume a longer time to re-treatment.

Similarly, the way in which patients discontinue rituximab in the BRAM model overestimates the QALY gains achievable with this therapy. Patients stopping rituximab due to adverse events or lack of efficacy accrue QALY gains until the next re-treatment cycle when they are taken off rituximab. These patients therefore have no HAQ worsening until the end of the re-treatment cycle whereas for all other therapies the time of switching and possible HAQ progression is applied immediately. This bias will be greater for longer intervals between rituximab re-treatment. In the base case it appears that all patients receiving rituximab will gain the benefit of 8.7 months without HAQ progression, including those who do not respond to treatment.

4.2 Calculation of drug costs in the BRAM model

Abbott is unsure whether the comments in this section accurately reflect how the costs are applied in the BRAM model due to our uncertainty regarding the following questions:

1. How are "start up" costs applied in the model and to what time period do they refer?

2. How are the "start up" costs and annual costs combined to give a first year's cost?

3. How is the cycle time for treatment related to the "start up" and annual costs for rituximab?

4.2.1 Annual Drug Costs

Table 79 of the Assessment Report shows the drug costs, along with dosing assumptions. The costs and assumptions for the three TNF inhibitors as reported in this table are shown below:

Table 4.2.1.1: Drug costs for adalimumab, etanercept and infliximab

Drug	Cost	Assumptions
Adalimumab	£357.50 per dose	26 doses per year
Etanercept	£178.75 per dose	52 doses per year
Infliximab	£1,258.86 per injection	70kg patient, drug wastage

Drug Costs

Based on these assumptions, the annual drug cost of both adalimumab and etanercept is £9,295. A 70kg patient would require 3 vials of infliximab per dose which results in a cost per dose of £1,258.86. Assuming that the annual drug cost refers to the maintenance dose (and induction doses are therefore excluded), an infliximab patient will require a dose every 8 weeks, corresponding to 7 doses per year. The annual drug cost of infliximab is therefore £8,182.59.

Administration Costs

On page 212, the Assessment Group reports that an administration cost of £141.83 is assumed for each dose of infliximab, which would result in an annual administration cost of £921.90. Adding this to the drug cost gives a total drug and administration cost of £9,104.49 for infliximab.

Monitoring Costs

Page 212/213 of the assessment report states that no additional monitoring costs are incurred for the biologics, since this will be included in the monitoring for methotrexate.

Total Annual Cost

Based on these calculations, the annual drug, administration and monitoring costs for each of the TNF inhibitors are shown in the table below alongside the annual drug costs used in the BRAM model and reported in Table 81 of the Assessment Report.

Table 4.2.1.2 Differences in annual costs in BRAM compared to Abbott assumptions

	Costs in Table 81 of the assessment report	Costs as per calculations in section 4.2	Difference
Adalimumab	£10,290.74	£9,295.00	£995.74
Etanercept	£10,290.74	£9,295.00	£995.74
Infliximab	£9,399.88	£9,104.49	£295.39

It can be observed from this table that the annual costs used in the BRAM are higher than those calculated as described above. This suggests that some additional costs have been included in the annual costs used in the model, although it is unclear what these costs are. It is noted that the calculated costs do not include methotrexate use, however since methotrexate dosing is the same for all of the TNF inhibitors, this would increase the annual cost for all of the TNF inhibitors equally which is not observed in the table above which shows that the difference in cost for infliximab is much lower than for adalimumab and etanercept.

4.2.2 Start Up Costs

Page 212 of the Assessment Report notes that the model includes "start up" costs reflecting higher dosage and additional monitoring early in treatment, and the start up costs for each treatment are shown in Table 81.

In this table, the start up cost for adalimumab is reported to be £382.03. However, since adalimumab does not have a loading dose early in treatment, and the model assumes no additional monitoring for biologic therapies, it is unclear what this cost relates to. Since the cost of etanercept is higher than that for adalimumab despite the fact that the two drugs have equal drug costs, it appears that the "start up" costs are being applied to different time periods, or are being calculated differently for each of the drugs.

Furthermore, infliximab dosing is administered at week 0, week 2, week 6 and every 8 weeks thereafter. Depending on how the start up cost is being applied in the model, this corresponds to at least two additional doses at the start of treatment. As discussed previously, according to the Assessment Report the drug cost per dose of infliximab is £1,258.86 and the cost per administration is £141.83 resulting in a total cost per dose of £1,400.69. However, the start up cost used in the model for infliximab is £1,720.44 which is significantly less than the cost of the induction doses.

Finally, as reported in Table 79 of the Assessment Report, the cost per 500mg vial rituximab is £873.15 and the required dosage is 2x1000mg per course resulting in a drug cost per course of £3,492.60. Adding the administration costs of £141.83 per administration results in a total cost per course of £3,776.26, which is incurred during the first 2 weeks of treatment. However, the start up cost of rituximab is reported to be only £319.75 in the BRAM. It is also unclear whether the requirement to co-administer rituximab with corticosteroids has been included in these cost calculations.

Since these start up costs do not appear to relate to induction costs, or costs incurred during a defined number of weeks of treatment, it is unclear how they have been calculated and how they are applied in the model.

Based on the preceding comments Abbott is unsure how the “start up” cost and “annual cost” inputs of the BRAM model should be adjusted to appropriately reflect the higher induction costs of treatment with rituximab and infliximab and to adjust the costs of adalimumab and etanercept to set them equal.

4.3 Data applied for drug stopping in the short term in the BRAM model

A variety of different data sources have been used to estimate short term stopping rates for the different drug therapies considered in this appraisal. In the absence of robust comparative data it would be preferable to model the short term discontinuation rates as equal for the different biologics.

5. Need for access to a sequence of effective treatment options for patients with severe RA

5.1 Need for sequence of effective biologic treatment options

It is necessary for patients to have access to a sequence of effective therapies to control the disease over their lifetime. Sequences of conventional DMARDs after failure of TNF inhibitors have no data to indicate that they will be effective in reducing disease progression in patients with moderate to severe disease. A sequence of therapy with multiple TNF inhibitors followed by biologics with other mechanisms of action is necessary to avoid progressive functional impairment which is associated with a low quality of life and high burden to patients, carers and the state. The need to consider the lifetime implications of sequencing of treatments is an important consideration for the cost effectiveness of RA patients. In the modelling results submitted by Abbott, the greatest QALY gain was achieved by patients receiving a sequence of two TNF inhibitors followed by rituximab.

5.2 Existence of negative utilities highlights the extreme impact of RA on quality of life

The Assessment Group highlights that the inclusion of negative utilities for the patient population has an important effect on the estimated cost-effectiveness. Available data indicate that a significant proportion of RA patients with high levels of functional impairment have negative utilities, that is their disease state is considered by the general population to be worse than death. These data highlight the severity of the target patient population being considered for these treatment options. Given the large improvements in quality of life that are achievable by treatment with biologic therapy options and the low starting quality of life, Abbott considers it is important to prioritise sequential biologic therapy options for this group of patients.

5.3 Preference for adalimumab observed in the survey of rheumatologists

Abbott considers that it is important to allow patients and clinicians the choice of the most appropriate drug treatment sequences for treating RA. The results of the survey of West Midlands rheumatologists highlight that there are many reasons why a particular biologic agent would be preferred over other therapy options. Furthermore, the survey results indicate a preference for patient choice (9 out of 27 respondents) in deciding which TNF inhibitor should be used first. Behind patient choice, the second most popular therapy option is adalimumab, noted by 7 out of 27 rheumatologists. When the question was posed as to which biologic would be chosen after failure of a TNF inhibitor, 17 respondents would wish to try a second TNF inhibitor. Nine respondents would try rituximab as a second line biologic agent and one would try tocilizumab.

These survey results indicate a clear preference among rheumatologists for using a 2nd TNF inhibitor rather than rituximab and are an important consideration given uncertainties regarding the effectiveness of rituximab in rheumatoid factor negative patients, the safety of biologic treatment after rituximab and the similar cost of TNF inhibitors and rituximab when rituximab re-treatment is given every 6 months, as necessary to maintain disease control.

6.0 Summary

In summary, Abbott considers that the following points are important considerations the Committee should consider when interpreting the Assessment Report:

- The effectiveness of conventional DMARDs have been overestimated in the BRAM model based on the available data.
- The long-term effectiveness and time on drug for the interventions under evaluation are derived from different sources without adjustment for potential biases in the data sources, which subsequently leads to the overestimation of QALYs gained for conventional DMARDs and rituximab.
- The optimal interval for re-treatment with rituximab remains to be determined for TNF failure patients in UK clinical practice. The BRAM model applies an 8.7 month re-treatment interval for rituximab in the base case and notes that the cost effectiveness of rituximab varies markedly based on the time to re-treatment. However, this analysis varied only the cost for rituximab and assumed that the effectiveness of rituximab is the same when given every 6 months or every 8.7 months, when evidence shows loss of disease control when the interval is greater than > 6 months.

- If an 8.7-month mean re-treatment interval is applied then this dosing regimen should be associated with commensurately lower QALY gains for rituximab, as patients losing response would suffer a reduction in their quality of life until re-treated.
- The safety of rituximab in patients with RA is not as extensive as the TNF inhibitors and there appears to be an increased risk of PML that needs to be taken into account in the modelling. Furthermore, there is limited experience regarding the safety of giving TNF inhibitors after rituximab therapy.
- Rituximab is less effective in RF- patients than it is in RF+ patients, particularly when radiographic progression is examined, which is not the case with the TNF inhibitors.
- It is unclear how some of the drug costs have been applied in the model, which needs to be clarified.
- There is a need for patients to have access to a sequence of effective therapies to control the disease over their lifetime. In the modelling results submitted by Abbott, the greatest QALY gain was achieved by patients receiving a sequence of two TNF inhibitors followed by rituximab.

References

[1] Van Vollenhoven R, Cifaldi M, Roy S et al. Relationship Between Radiographic Damage and Employment Over Time in Patients with Early Rheumatoid Arthritis (RA): Results From the PREMIER Health Economic Companion Study DE032. ACR Conference 2009 Poster presentation 66.

[2] Aletaha D, Stamm T, Kapral T et al. Survival and effectiveness of leflunomide compared with methotrexate and sulfasalazine in rheumatoid arthritis: a matched observational study. Ann Rheum Dis. 2003 Oct;62(10):944-51.

[3] Keystone E, Fleischmann R, Emery P, Furst DE, van Vollenhoven R, Bathon J, Dougados M, Baldassare A, Ferraccioli G, Chubick A, Udell J, Cravets MW, Agarwal S, Cooper S, Magrini F. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. *Arthritis Rheum*. 2007 Dec;**56**(12):3896-908.

[4] Emery P, Mease PJ, Rubbert-Roth A et al. Re-treatment with Rituximab (RTX) Based On a Treatment to Target (TT) Approach Provides Better Disease Control Than Treatment as Needed (PRN) in Patients (pts) with Rheumatoid Arthritis (RA). ACR Conference 2009. Poster presentation 2013

[5] NICE Rheumatoid Arthritis Clinical Guideline CG79: The management of rheumatoid arthritis is adults. Issue date February 2009.

[6] Smolen J, Keystone E, Emery P, Breedveld F, Betteridge N, Bumester G *et al.* Consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Annals of Rheumatic Disease* 2007;**66**;143-150.

[7] Electronic Medicines Compendium. Summary of Product Characteristics for rituximab (MabThera). Last accessed 7 August 2009.

[8]http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm187791.htm

[9] Direct Healthcare Professional Communication on rituximab (Mabthera) and progressive multifocal leucoencephalopathy (PML) in patients treated for rheumatoid arthritis. Roche Products (Ireland). 9 November 2009.

[10]FDA Black Box warnings (www.FormWeb.com): Rituximab.
http://www.formularyproductions.com/master/showpage.php?dir=blackbox&whichpage=147

[11] Carson KR, Evens AM, Richey EA et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood. 2009 May 14;113(20):4834-40. Epub 2009 Mar 5.

[12] Carson KR, Focosi D, Major EO et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. Lancet Oncol. 2009 Aug;10(8):816-24.

[13] van Vollenhoven R, Emery P, Bingham CO et al. Long-Term Safety of Rituximab: Long-Term Follow-up of the RA Clinical Trials and Re-treatment Population. ACR 2009 conference. Poster presentation 1952.

[14] Genovese MC, Breedveld FC, Emery P et al. Rate of serious infections in rituximab treated patients with rheumatoid arthritis that subsequently receive other biologic therapies. EULAR Conference 2009. Poster presentation SAT0097.

[15] Genovese MC, Breedveld FC, Emery P, Moreland L, Keystone E, Matteson E, Baptiste Y. Safety of TNF inhibitors and non-biologic DMARDs in rheumatoid arthritis patients previously treated with rituximab. 71st American College of Rheumatology Annual Scientific Meeting, Boston, MA, USA, 6-11 November 2007.

[16] Hyrich KL, Watson KD, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford). 2006 Dec;**45**(12):1558-65.

[17] Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, Clinical and Functional Outcomes With Adalimumab (a Human Anti-TNF Monoclonal Antibody) in the Treatment of Patients With Active Rheumatoid Arthritis on Concomitant Methotrexate Therapy: A Randomized, Placebo-Controlled, 52-Week Trial. Arthritis Rheum 2004; **50**(5):1400-1411.

[18] http://www.roche.com/irp090612_eular.pdf

[19] www.roche.com/irp090612_eular.pdf

[20] Isaacs JD, Olech E, Tak PP et al. Autoantibody-positive rheumatoid arthritis (RA) patients (pts) have enhanced clinical response to rituximab (RTX) when compared with seronegative patients. EULAR 2009 conference. Poster presentation FRI0256.

[21] Van Vollenhoven R, Chatzidionysiou K, Nasonov E et al. Six-Month Results From the Collaborative European REgistries for Rituximab in Rheumatoid Arthritis (CERERRA). Efficacy of Rituximab Is Highest in RF-Positive Patients and in Those Who Failed at Most One Prior Anti-TNF. ACR Conference 2009. Poster presentation 1671.

National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by the West Midlands Health Technology Assessment Collaboration. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Acknowledgement and Undertaking Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. You must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results

calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

November 2009

Issue 1 Annual Drug Costs

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The annual drug costs applied in the model do not reflect the drug acquisition cost over a 12 month period, as calculated using the unit costs and dosing assumptions reported in table 79 of the Assessment Group Report. If the annual costs used in the model are in fact correct, it is unclear exactly how the annual drug costs are applied in the model.	Due to this lack of clarity, Abbott has been unable to confirm whether the results presented in the Assessment Group Report are correct.	The annual costs applied in the model for adalimumab appear to be higher than the actual drug acquisition cost (£10,290.74 vs. £9,295). If the costs used in the model are incorrect, the total cost for adalimumab would be reduced, this reducing the cost/QALY of adalimumab vs. DMARDs.

Issue 2 Start up Costs

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model includes start up costs for each treatment. However, these costs do not appear to relate to induction costs, or costs incurred during a defined number of weeks of treatment. It is therefore unclear how they have been calculated and how they are applied in the model.	When combined with the issues around the annual drug costs (see issue 1 above) Abbott is unsure how the “start up” cost and “annual cost” inputs of the BRAM model should be adjusted to appropriately reflect the higher induction costs of treatment with rituximab and infliximab and to adjust the costs of adalimumab and etanercept to set them equal.	Since Abbott is unclear as to how these costs are being applied in the model, we were unable to investigate the impact of different cost assumptions on the results or to ascertain whether the model produces reliable estimates of the cost-effectiveness of the therapies under consideration.

Issue 3 HAQ multipliers

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Result of amended model or expected impact on the result (if applicable)</th></tr>
<tr>
<td>Since the model uses HAQ scores as the marker for disease severity, the change in HAQ on starting a treatment is a key model input. However, the HAQ multipliers used in the BRAM are based on separate sources, with no adjustment for the differences in these populations.</td>
<td>
In line with the NICE methods for technology appraisals, Abbott conducted a mixed treatment comparison which synthesised evidence from a large number of trials and takes into account the effect of giving treatments after failure of a TNF inhibitor.

Based on this analysis, the following HAQ multipliers were applied in the model:

<table>
<tr><th></th><th>adalimumab</th><th>DMARDs</th></tr>
<tr><td>new mean</td><td>0.362</td><td>0.169</td></tr>
<tr><td>assumed variance</td><td>0.1</td><td>0.1</td></tr>
<tr><td>new alpha</td><td>0.474</td><td>0.068</td></tr>
<tr><td>new beta</td><td>0.835</td><td>0.336</td></tr>
</table>
These multipliers are more representative of the expected effectiveness of each drug in the population of interest for this appraisal

Since no scenario analysis were presented in the assessment group report using different HAQ multipliers, several scenario analyses were also conducted in order to validate whether the model is applying the HAQ multipliers appropriately. The following analyses were considered:

<u>Analysis 1</u>

HAQ multipliers set at 25% for all conventional DMARDs

<table>
<tr><th></th><th>Alpha</th><th>Beta</th><th>Mean</th></tr>
<tr><td>Leflunomide</td><td>0.123664611</td><td>0.935080729</td><td>0.116803</td></tr>
<tr><td>Gold</td><td>0.100292181</td><td>0.924917252</td><td>0.097826</td></tr>
</table>
</td>
<td>
As be seen from the results of this analysis presented below, the HAQ multipliers are a key model input. Using more appropriate values for the HAQ multipliers has a large impact on the results, with the ICER for adalimumab vs. DMARDs falling from £34,300 in the reference case to £25,900.

<table>
<tr><th>Treatment</th><th>Mean Cost</th><th>Mean QALY</th><th>ICER</th></tr>
<tr><td>ADA</td><td>74200</td><td>2.96936774</td><td></td></tr>
<tr><td>DMARDs</td><td>49100</td><td>1.99752626</td><td></td></tr>
<tr><td>ICER</td><td></td><td></td><td>£25,900</td></tr>
</table>
The results of the scenario analyses are presented below. As would be expected, reducing the HAQ multiplier for conventional DMARDs improves the cost-effectiveness of adalimumab.

<table>
<tr><th>Treatment</th><th>Mean Cost</th><th>Mean QALY</th><th></th></tr>
<tr><td><u>Analysis 1</u></td><td></td><td></td><td></td></tr>
<tr><td>ADA</td><td>£76,028</td><td>2.292</td><td></td></tr>
<tr><td>DMARDs</td><td>£50,824</td><td>1.3924</td><td></td></tr>
<tr><td>ICER</td><td></td><td></td><td>£28,017</td></tr>
<tr><td><u>Analysis 2</u></td><td></td><td></td><td></td></tr>
<tr><td>ADA</td><td>£75,923</td><td>2.3321</td><td></td></tr>
<tr><td>DMARDs</td><td>£50,540</td><td>1.4509</td><td></td></tr>
<tr><td>ICER</td><td></td><td></td><td>£28,805</td></tr>
</table>
</td>
</tr>
</table>

	Ciclosporin	0.029544598	0.324991928	0.083333015	Analysis 3			
	Azathioprine	0.047368218	0.899996138	0.05	ADA	£74,226	2.6629	
	Analysis 2				DMARDs	£48,312	1.8557	
	HAQ multipliers for all conventional DMARDs set equal to azathioprine (alpha= 0.10, beta = 0.90, mean = 0.10)				ICER			£36,131
	It was anticipated that some of the differences between adalimumab and conventional DMARDs may be due to the different withdrawal rates. Therefore in order to accurately assess the true impact of the changes in HAQ multipliers, further scenario analyses were conducted in which the HAQ multipliers were varied as in analyses 1 and 2, but the Weibull drug survival for conventional DMARDs was set equal to that for adalimumab.				Analysis 4			
					ADA	£75,513	2.2042	
					DMARDs	£49,946	1.2775	
					ICER			£27,589
	Analysis 3: Reference case HAQ multipliers plus DMARD long-term survival = adalimumab				Analysis 5			
					ADA	£75,366	2.2456	
					DMARDs	£49,833	1.331	
	Analysis 4: Analysis 1 plus DMARD long-term survival = adalimumab				ICER			£27,917
	Analysis 5: Analysis 2 plus DMARD long-term survival = adalimumab							

Issue 4 No HAQ progression on rituximab despite evidence of worsening disease severity between courses

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Result of amended model or expected impact on the result (if applicable)</th></tr>
<tr>
<td>The reference case analysis assumes that patients receive further courses of rituximab every 8.7 months. However, the model also assumes that during this period patients experience no HAQ progression. This assumption is not supported by the published literature, which indicates that rituximab patients experience a loss of efficacy after the initial 6 months.</td>
<td>The model structure is not designed to allow for this worsening of disease severity between courses.

Two analyses were run in order to assess the potential impact of this issue:

<u>Analysis 1</u>

Annual HAQ progression for rituximab was set to 0.02 (or 6.5 years on average to 0.125 change in HAQ)

<u>Analysis 2</u>

In line with a sensitivity analysis conducted by the assessment group which used a 0.03 increase per annum, the annual HAQ progression for RTX was set to 0.03 (or 4 years on average to 0.125 change in HAQ).</td>
<td>As can be seen in the tables below, this issue appears to have a significant impact on the cost-effectiveness of rituximab vs. conventional DMARDs, with the ICER rising from £21,200 in the reference case to £33,200 in analysis 1, and £34,300 in analysis 2.

<u>Analysis 1</u>

<table>
<tr><th>Treatment</th><th>Mean Cost</th><th>95% Credible Interval</th><th></th><th>Mean QALY</th><th>95% Credible Interval</th><th></th></tr>
<tr><td>RTX</td><td>69700</td><td>62600</td><td>77300</td><td>2.772036</td><td>-2.5506</td><td>7.7031</td></tr>
<tr><td>DMARDs</td><td>48800</td><td>42900</td><td>54600</td><td>2.142225</td><td>-3.42158</td><td>7.395075</td></tr>
<tr><td>Comparison</td><td>ICER</td><td>95% Credible Interval</td><td></td><td>£20,000/QALY</td><td>£30,000/QALY</td><td></td></tr>
<tr><td>RTX - DMARDs</td><td>33200</td><td>19300</td><td>81900</td><td>0.031</td><td>0.358</td><td></td></tr>
</table>

<u>Analysis 2</u>

<table>
<tr><th>Treatment</th><th>Mean Cost</th><th>95% Credible Interval</th><th></th><th>Mean QALY</th><th>95% Credible Interval</th><th></th></tr>
<tr><td>RTX</td><td>74400</td><td>68200</td><td>80700</td><td>2.89108</td><td>-2.20905</td><td>7.738125</td></tr>
<tr><td>DMARDs</td><td>48800</td><td>43100</td><td>54900</td><td>2.141906</td><td>-3.39618</td><td>7.423075</td></tr>
<tr><td>Comparison</td><td>ICER</td><td>95% Credible Interval</td><td></td><td>£20,000/QALY</td><td>£30,000/QALY</td><td></td></tr>
<tr><td>RTX - DMARDs</td><td>34300</td><td>21000</td><td>78100</td><td>0.17</td><td>0.658</td><td></td></tr>
</table>
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</tr>
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(please cut and paste further tables as necessary)