1 Executive summary

Background

Rheumatoid Arthritis (RA) is the most common inflammatory polyarthropathy in the UK affecting between 0.5% and 1% of the population. The mainstay of RA treatment interventions to date involve the use of disease modifying anti-rheumatic drugs (DMARDs) and tumour necrosis factor inhibitor (TNF) therapies. However, the effectiveness of these agents is often lost after a period of time and some patients suffer treatment induced side effects resulting in discontinuation. This can happen in approximately 25 - 50% of all patients treated and therefore a significant patient population exists with severe RA disease that has failed TNF inhibitor therapy.

It has been hypothesised that biological differences between the three currently marketed TNF inhibitors may provide a rationale to support sequential use. However, in the public domain there is a paucity of robust clinical evidence and outcomes data to support this hypothesis when treatment failure is due to lack of efficacy. Consequently there remains a significant amount of uncertainty around the clinical effectiveness of second anti-TNF usage.

Roche presents in this submission randomised controlled trial data to support the use of rituximab following a first anti TNF failure further supported by data from observational studies. These data establish the case for the clinical effectiveness of rituximab and when considered alongside the compelling economic case presented in this submission driven in part by the relatively low acquisition cost for rituximab, establishes with certainty the cost effectiveness of rituximab usage after one anti-TNF.

Rituximab

Rituximab is a monoclonal antibody that depletes the $CD20^+$ B cells implicated in the immunopathogenesis of RA. Rituximab was granted a marketing authorisation on 6th July 2006 for the following indication: *rituximab in combination with methotrexate is indicated for the treatment of adult patients with severe active RA who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs including one or more anti-tumour necrosis factor inhibitor therapies*".

The recommended dosage of rituximab is 1,000mg by IV infusion followed by a second 1,000mg IV infusion two weeks later. Repeat treatment with subsequent courses of rituximab is based on a clinical decision based on RA signs and symptoms. According to the marketing authorisation, retreatment of patients is expected to occur within 6 to 12 months. Pooled data from an extension of the registration study in which 279 patients had been retreated with rituximab at least once, showed that 63% received repeat treatment within 6-12 months of their first treatment course but more than a third of patients did not require re-treatment for more than a year. UK rituximab market research data collected following the publication of NICE TA126 in August 2007 indicates that the repeat treatment interval is presently 8.7 months. One course of rituximab (2x 1000mg) costs £3,492.60 and therefore assuming a repeat treatment every 8.7 months (including the impact of non-responders), gives an average annual drug cost for rituximab treatment of £4,817 pro rata.

Demonstrating Clinical Effectiveness

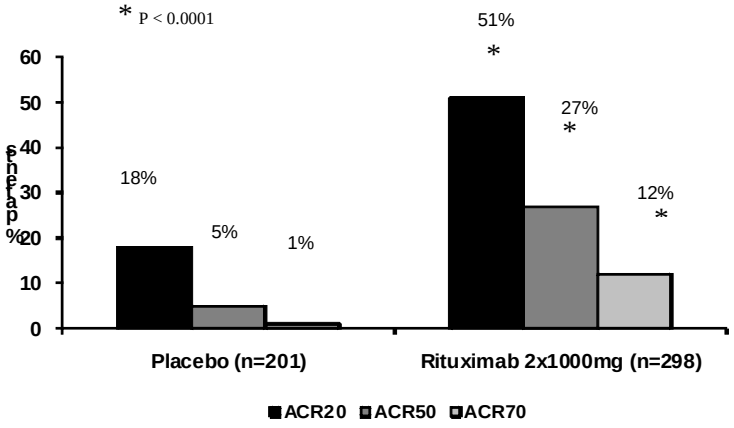
The clinical effectiveness section of this submission presents evidence supporting the use of rituximab after the failure of one anti-TNF from the phase III randomised study (REFLEX), its open label extension trial and other relevant publications.

Rituximab Phase III RCT – REFLEX

REFLEX, WA17042, was a multinational, randomised, double-blind, placebo-controlled, parallel group study in adult patients with moderate to severe active RA who had previously experienced an inadequate clinical response to treatment with anti-TNF inhibitor therapies.

Of the 520 patients who were enrolled in the study, 517 received at least part of a rituximab or placebo infusion and comprised the safety population. The primary endpoint of the study was ACR20 at week 24.The proportion of ACR20 responders at week 24 was significantly higher in the rituximab + MTX group than in the placebo + MTX group (51% vs 18%, respectively; (p<0.0001), Figure 1. . Logistic regression analysis showed that rituximab treated patients were 5 times more likely to achieve an ACR20 response than placebo-treated patients. Rituximab + MTX was more effective than placebo + MTX in all ACR response categories (p< 0.0001).

Figure 1: ACR response rates at 6 months, ITT population (REFLEX)

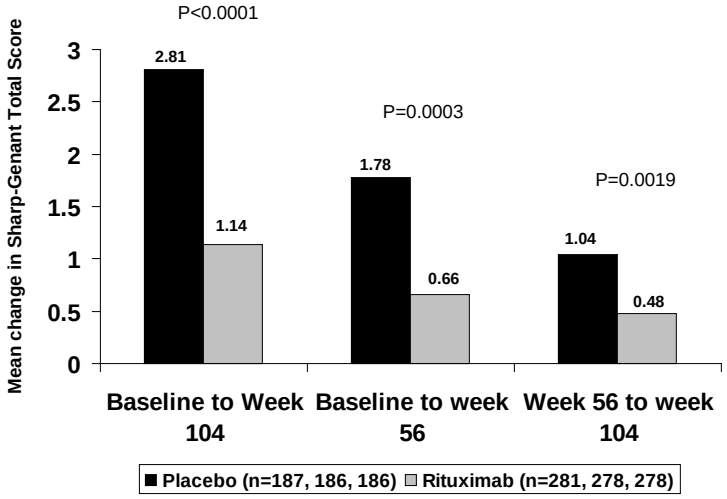


The ACR response rates resulting from the REFLEX trial were used in a mixed treatment comparison in order to adjust for the variation in placebo responses observed across the relevant studies. These adjusted ACR rates have been used in the cost effectiveness section of this submission.

Secondary endpoints of the trial included DAS28 and EULAR amongst others. Mean DAS28 score reduction from baseline in the rituximab + MTX group was significantly greater than in the placebo + MTX group; -1.9 vs -0.4 for rituximab vs placebo, respectively (p< 0.0001). At week 24, 2% of patients in the placebo + MTX group were considered to have low disease activity and none had achieved clinical remission. In comparison, in the rituximab + MTX group 15% of patients had low disease activity and 9% were in clinical remission. EULAR scores were also found to be significantly better in the rituximab arm compared to the placebo arm.

Radiographic data

The radiographic dataset for rituximab is unique in that it provides the only placebo-controlled evidence available on slowing of radiographic progression in anti-TNF-IR patients. The dataset was generated from REFLEX and its open-label extension, WA17531. The data show the reduction in the progression of joint damage in adult patients with active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs including one or more TNF inhibitor therapies.

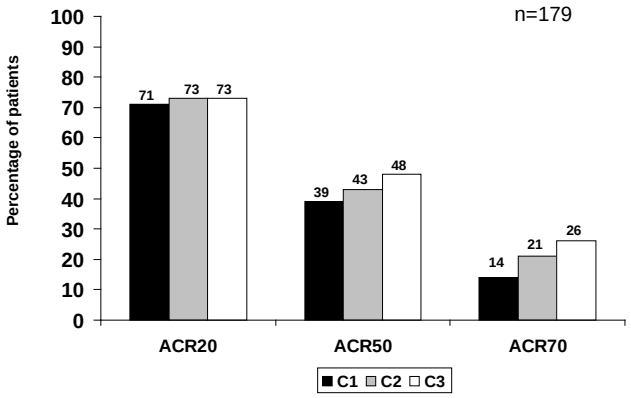


Efficacy of repeat treatment

Responding patients from the phase III RCT entered an open label extension study. Patients received repeated open-label treatment courses of the same rituximab regimen. Placebo patients in the original study were also eligible to enter and received their first course of rituximab within the extension study. Efficacy was determined according to original baseline.

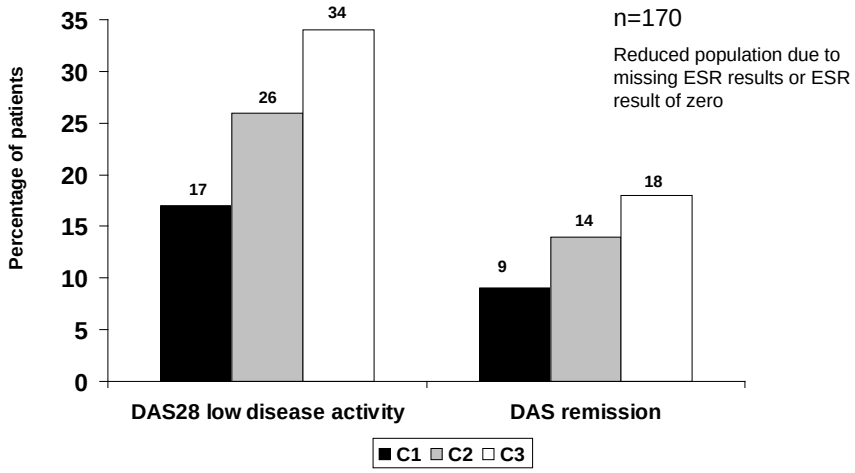
ACR20, 50, and 70 scores at 24 weeks following C1, C2, and C3 showed that repeated treatment with rituximab was effective over multiple courses. ACR20 responses at Week 24 following each course were maintained or increased with subsequent courses. ACR50 and ACR70 responses improved with overall ACR70 responses increasing from 14% following C1 to 26% following C3.

ACR response at Week 24 after three rituximab treatment courses (vs original baseline)



The proportion of patients with a EULAR response was comparable for C1 to C3 with over 80% of patients achieving a EULAR good/moderate response with each course. The proportion of patients achieving a EULAR good response showed an increase with each treatment course (C1, 17%; C2, 26%; C3, 34%)

Sustained improvement in DAS28 low disease activity and remission was also observed during C2 and C3, with remission rates increasing from 8.8% to 17.6% from C1 to C3.



The long-term extension study showed that, in patients with active RA and an inadequate response to TNF inhibitors, repeated courses of rituximab showed a comparable degree of sustained efficacy relative to original baseline.

Safety

Rituximab has been used in RA for about three years, however since 1998 when rituxumab was first licenced to treat non-Hodgkin's Lymphoma (NHL) more than 1,000,000 patients have been treated to date in both settings. The safety profile of rituximab in RA is shown in this submission to be comparable to that of the anti TNF inhibitors.

Demonstrating Cost Effectiveness

Rituximab in combination with methotrexate was shown to be cost effective in NICE TA126. Although many of the parameters used in the economic model for this submission have been kept the same as for TA126, Roche has improved upon the evidence base by updating several aspects of the economic model with the latest data cut-off from rituximab's Phase III extension trial and by utilising published advances in RA economic modelling.

In the cost effectiveness evaluation, rituximab is systematically compared to the anti-TNFs, abatacept and tDMARDs. In order to perform these pairwise comparisons and in the absence of head-to-head clinical data several standard methodologies were employed which are described in the submission. The sequences compared in this evaluation are shown in the table below.

Table 1: Comparator treatment sequences

Intervention sequence	**Comparator sequence**				
	A	**B**	**b**	**d**	**E**

i. Rituximab ii. Leflunomide iii. Gold iv. Cyclosporine v. Palliative care	i. Etanercept ii. Leflunomide iii. Gold iv. Cyclosporine v. Palliative care	i. Adalimumab ii. Leflunomide iii. Gold iv. Cyclosporine v. Palliative care	i. Infliximab ii. Leflunomide iii. Gold iv. Cyclosporine v. Palliative care	i. Abatacept ii. Leflunomide iii. Gold iv. Cyclosporine v. Palliative care	i. Leflunomide ii. Gold iii. Cyclosporine iv. Palliative care

Please note that Roche has not further performed any economic analysis for tocilizumab in this appraisal because this drug is the subject of a separate ongoing NICE single technology appraisal which will continue after the UK price of tocilizumab has been set and the drug launched in the UK.

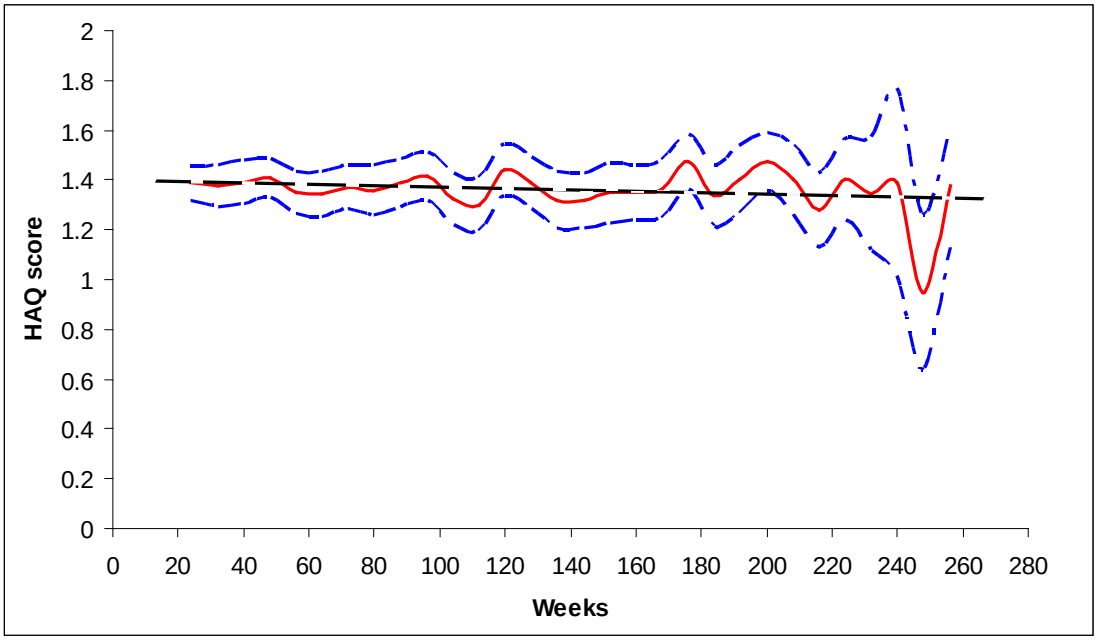
Model Design

The economic model utilised is consistent with that used in NICE TA126. ACR response categories define the size of the initial HAQ drop, utilising the rates derived from an MTC. An “individual simulation model” tracks the individual characteristics of patients and maintains a record of HAQ change for the duration that patients stay within the model. To inform patient HAQ change the model utilises the rituximab clinical trial data for the duration that this is available. Total direct NHS costs, QALYs and ICERs were estimated for all pairwise comparisons of rituximab with each of the interventions.

HAQ Change Over Time

A key clinical parameter driving the cost effectiveness of RA therapies is the assumed long term HAQ change for a responding patient. For the purposes of this evaluation, Roche utilised as long a follow-up from the rituximab phase III study as was possible in order to minimise uncertainty in the estimation of this key parameter. Contrary to previous conclusions (in both TA126 and in the previous MTA of the cycling of anti-TNFs), patients remaining on rituximab illustrated a sustained physical functioning (i.e. HAQ slope equal to zero) for the duration of the trial follow-up. Long term HAQ for anti-TNFs and abatacept was assumed to be equal to zero.

Figure 2: Long term HAQ change for rituximab patients remaining on therapy (REFLEX extension population)



Results

The mean incremental costs and QALYs gained for the pairwise comparisons between rituximab containing regimens and regimens that contain one of the other interventions are presented below.

Table 2: Cost effectiveness results. **Negative cost values indicate that rituximab is cost saving, negative effectiveness/QALY values indicate that rituximab is less effective than comparator**

rituximab **vs etanercept**	
Incremental Costs	Incremental QALYs
-£13,246	0.0168
rituximab dominates	
rituximab **vs infliximab**	
Incremental Costs	Incremental QALYs
-£10,490	0.0699
rituximab dominates	

rituximab **vs abatacept**	
Incremental Costs	Incremental QALYs
-£16,075	0.0606
rituximab dominates	
rituximab **vs adalimumab**	
Incremental Costs	Incremental QALYs
-£13,551	-0.0436
ICER: £310,771 per QALY	
rituximab **vs tDMARDs**	
Incremental Costs	Incremental QALYs
£6,323	1.075
ICER: £5,311 per QALY	

Rituximab compared to anti-TNFs

Rituximab is a more effective and cost saving treatment compared to etanercept and infliximab when these treatments are assessed in TNF-IR. Probabilistic sensitivity analysis (PSA) demonstrated that rituximab was found to dominate each of the two treatments in ~70% of simulations and to be cost effective in 100% of simulations. Rituximab was found to be marginally less effective in the deterministic results but also less costly than adalimumab in the base case. The incremental benefit of adalimumab against rituximab was 0.0436 QALYs. In probabilistic sensitivity analysis, rituximab was found to be cost effective and dominant against adalimumab in 100% of simulations and more effective and less costly in 37% of iterations.

In order to assess the sensitivity of the results of rituximab versus anti-TNFs, Roche conducted a scenario analysis in which rituximab response rates were kept the same as in the base case but the response rates for the anti-TNFs were increased to the level of those observed for anti TNFs in the DMARD-IR (TNF naïve-patients) trials.

This analysis demonstrated that the anti-TNFs would need to show better efficacy in TNF-experienced (TNF-IR) patients than those currently demonstrated in TNF-naïve (DMARD-IR) patients in order to be cost effective against rituximab.

Rituximab compared to abatacept

Rituximab was found to be more effective and less costly than abatacept. In PSA, rituximab was cost effective compared to abatacept in 100% of iterations and dominated abatacept in 70% of iterations.

Rituximab compared to tDMARDs

Rituximab was found to be more effective and more costly in the base case. The ICER for this comparison was £5,311 per QALY with rituximab treatment generating an incremental benefit of 1.075 QALYs at an additional cost of £6,323. In PSA, rituximab was demonstrated to be cost effective in 100% of iterations.

Conclusion

Roche has demonstrated in this submission that rituximab provides at least equivalence in efficacy compared to the anti-TNF inhibitors and to abatacept. Clinical benefits have been illustrated well beyond the initial six month trial with stable disease being confirmed by a flat HAQ change whilst patients remain on rituximab treatment.

Furthermore, updated economic analysis using the most up to date evidence base available supported by deterministic and probabilistic sensitivity analyses confirms that rituximab is a cost effective use of NHS resources and should therefore be recommended for use after one anti TNF treatment.