Health Technology Appraisal
Golimumab for the treatment of Rheumatoid Arthritis after the failure of previous disease-modifying anti-rheumatic drugs.
Pfizer response to the golimumab ACD

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Pfizer welcomes the opportunity to comment on the ACD and the evaluation report for golimumab for the treatment of Rheumatoid Arthritis after the failure of previous disease-modifying anti-rheumatic drugs. Overall we agree that the provisional recommendations for golimumab for this indication are sound and are a suitable basis for guidance to the NHS. However, we have some concerns regarding the summaries of clinical and cost effectiveness evidence for the DMARD experienced population considered in the ACD and evaluation report.

In particular, our concerns are related to the scope, inclusion/exclusion criteria and the resultant trials considered within the basecase DMARD experienced population meta-analyses/MTC and sensitivity analyses, and also the failure to include ACR 70 response within the economic analyses. These concerns are summarised below:

1. **The inclusion of the etanercept Tempo (Klareskog et al 2004) trial in the basecase**

2. **The addition of monotherapy trial data in the evidence base for comparator TNF inhibitors**

3. **The inconsistency of the trials included in the ACR 70 response analyses**

We recognise that the first two concerns have been explored **separately** in sensitivity analyses by the manufacturer. However, we believe that this is insufficient and that the manufacturers' basecase analysis should exclude **both** the TEMPO trial and monotherapy trials from the meta-analysis/MTC, as these trials are likely to be fundamentally different from the other combination therapy trials in this review. The reasons for this rationale are detailed in sections 1 and 2 below.

In addition, we have identified a number of issues/errors in our review of the evaluation report and these are summarised in appendix 1, page 3 of our response.

1. **The inclusion of the etanercept Tempo (Klareskog et al 2004) trial in the basecase**

Pfizer notes in section 3.18, p.11 of the ACD, that a sensitivity analysis has been undertaken by the manufacturer in their meta-analysis/ MTC in which the TEMPO trial has been excluded. The results of the sensitivity analysis are presented below and show an increased efficacy for etanercept:

'the exclusion of the TEMPO trial resulted in raised relative risks for ACR20 and ACR50, indicating increased efficacy for etanercept in comparison with golimumab. However, these results were statistically significant only in the fixed effects model for the ACR20 response. Exclusion of the TEMPO trial also altered the relative estimates for golimumab in comparison with the other treatments.' (p.11 of the ACD)

Whilst we agree with this approach of removing the TEMPO study in this sensitivity analysis, we would recommend that the TEMPO trial is excluded from the basecase analysis as this trial is fundamentally different from all comparator TNF trials in this analysis since patients did not need to have demonstrated an adequate response to methotrexate at baseline. Therefore these patients were more likely to benefit from MTX and as a result the observed placebo response reported in this trial was higher than in other biological DMARD trials.

Furthermore, NICE in previous published appraisals for RA treatment (tocilizumab TA198 and certolizumab pegol TA186) has noted that the TEMPO trial was different from other TNF trials because of the unusually high placebo response rate and has requested that it should be excluded from the analysis. Therefore, to be consistent this trial needs to be removed from the analysis.

2. **The addition of monotherapy trial data in the evidence base for comparator TNF inhibitors**

From a review of the evaluation report we note that the inclusion criteria for the manufacturer's DMARD experienced population MTC allows for both combination and monotherapy trial data to be synthesised in the evidence base for the comparator TNF inhibitors. We disagree with this approach for the reason that golimumab is not licensed as a monotherapy treatment and therefore comparison of golimumab combination therapy alone versus combined monotherapy and combination therapy data for comparator TNFs leads to a bias in the data considered. Moreover, the addition of monotherapy trials will lead to increased heterogeneity in the trial population and increases the uncertainty of the results produced.

Accordingly, we would recommend that the following monotherapy trials are removed from the basecase analysis:

- Van der Putte et al [2004], adalimumab
- CHANGE, adalimumab
- Moreland et al [1999], etanercept

Based on this revised inclusion criteria described above we would argue that the monotherapy arm of the etanercept Combe trial can no longer be included in the analysis leaving just the placebo and etanercept plus sulfasalazine arms eligible for

inclusion in the meta-analyses/MTC. Furthermore, we realise that the Combe trial meets the inclusion of the scope, but we feel it is important to note that this trial considers the use of etanercept in combination with sulfasalazine which does not reflect the UK licensed indication.

3. The inconsistency of the trials included in the ACR 70 response analyses.

Pfizer agrees with the statement section 1.4 that the ACR 70 should be included within the economic analysis. However, we would like to ensure that a consistent approach is taken to generate these estimates within the meta-analyses and MTC. Specifically, we have observed that the ACR70 response data submitted as part of the clarifying questions from the manufacture to the ERG excluded infliximab trial (Maini et al 1998) and the etanercept TEMPO trial from the analyses, which is different from the basecase ACR 20 and 50 response data. Whilst we agree that the TEMPO trial should be removed from all ACR analyses, we would like further clarification why the Maini trial has been removed.

Appendix 1 – Minor errors/issues presented in the evaluation report

Study/Studies	Comment
Combe et al (2006)	• In the manufacturer's meta-analysis and MTC results in table 27, p.68 the etanercept plus placebo arm was added to the etanercept plus sulfasalazine. This breaks randomisation and the two arms should be considered separately. • Number of patients in the treatment arm is different for ACR20, Table 18, p61 compared to ACR50, Table 19, p.63.
Chen (2009) and Abe (2006)	• The MTC ***may have*** included data at 12/14 weeks (Chen 2009 and Abe 2006) though the majority of studies included in the MTC reported results at 24 weeks. [Chen and Abe were not included in the direct meta-analysis (section 5.5.4 of submission). However, Table 54, p.78 lists Chen and Abe as studies included in the MTC analysis of DMARD-experienced population.
Weinblatt et al (1999)	• Table 18, p.61 of the manufacturer's submission states that in the active arm 71 out of 59 patients had an ACR 20 response. In the placebo arm 27 out of 30 patients had an ACR 20 response. These estimates do not match the data listed in table 27 of the manufacturer's submission (42 out of 59 and 8 out of 30).
RAPID 1 and RAPID 2	We would like to highlight that the efficacy estimates of certolizumab pegol with methotrexate in the MTC may lead to an overestimation of its benefit and these should be treated with caution due to the uncertainty around its true benefit. • Patients are excluded 8 weeks before the primary efficacy endpoint and treated as non responders. However in these 8 weeks it is possible that some patients would have achieved an ACR20 response and were incorrectly assumed to have a no response. This is likely to affect the control arm to a greater extent due to the higher withdrawal rate (63-81%) compared to the intervention arms (17-21%). • It has been shown that methotrexate is most effective when step-up therapy is employed (as it is in the majority of other trials). The restriction on dose increases may have resulted in patients being taken into rescue therapy from the control arm that

	would have responded by week 24. This would result in a greater difference between certolizumab pegol efficacy and that seen in the control arm.
ATTRACT	• In the direct analysis some treatment arms appear to have been added together incorrectly: e.g. for ATTRACT, Table 44, p.74 it should be 47 out of 86 not 47 out of 172, as this is the total number of patients for Infliximab 3 mg/kg every 8 weeks plus MTX arm added to Infliximab 3 mg/kg every 4 weeks plus MTX.
SATORI and Abe (2006)	• SATORI and Abe 2006 have concomitant methotrexate doses of 8 and 7.1mg/week respectively, which is considerably lower than other studies used for MTX. This is due to low maximum methotrexate doses in many East Asian countries and do not offer appropriate comparison. • In the Abbot Laboratories comment on the certolizumab pegol appraisal it is noted that important clinical characteristics and patient demographics in East Asian studies are very different to the UK RA patient population. It is therefore important to consider such trials in sensitivity analysis.
General issues	• No justification for the inclusion of the median RR rather than the mean RR in the economic model. • We have no additional comments on the economic model.