[redacted]

Thursday 25th March 2010

[redacted]
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

**BY E-MAIL**

Dear [redacted],

## SINGLE TECHNOLOGY APPRAISAL – Tocilizumab for the treatment of rheumatoid arthritis

Thank you for sending us the Appraisal Consultation Document (ACD) for the tocilizumab technology appraisal. Roche is disappointed that the Appraisal Committee has not recommended tocilizumab when evaluating the available clinical and cost effectiveness evidence.

Given the volume of information and detail required to fully address all the issues arising from the ACD, an executive summary is included at the front of our main response which is subsequently provided under the four standard headings below.

Roche's response to the 3rd ACD focuses upon 2 main issues:

1. Patient benefit, total NHS costs and therefore the cost effectiveness of tocilizumab is similar, irrespective of its position in the treatment algorithm

2. There is a clear clinical need to have a new therapeutic class as an additional option in the management of RA in the UK

Please do not hesitate to contact us should you require any further information or clarifications.

Yours Sincerely,

[redacted]

# Executive Summary

## 1 Roche welcomes the Committee's conclusions that improvements in the future management of RA relies upon the addition of innovative medicines to the current treatment algorithms

Section 4.21 of the ACD: "*The Committee was aware of the manufacturer's argument that a major benefit was that a sequence of three biological treatments would be better than two. This was because an additional treatment in the sequence with a different mode of action resulted in an extra option for targeted therapy, potentially delaying disease progression for much longer.*"

This principle is reflected in the scenarios in which tocilizumab is given as an addition to the existing treatment pathway. To clarify, by evaluating these scenarios Roche is not seeking to displace any treatments currently used in the treatment of RA or for NICE guidance to provide a definitive treatment pathway that explicitly clarifies the position of tocilizumab. Instead Roche has aimed to demonstrate that tocilizumab is a cost effective treatment irrespective of the position it occupies in the treatment algorithm and therefore clinicians can be permitted to determine its optimum position, within its licensed indications.

## 2 Tocilizumab is a cost effective option when added into the current standard of treatment, irrespective of its position in the treatment algorithm

Roche provides an analysis that demonstrates that tocilizumab is a cost effective option when added to the current standard of care, irrespective of the position it is being used. By comparing the 3 alternative biologic treatment strategies of interest to the committee, illustrated in table 1 below, it can be seen that the total costs to the NHS and patient benefits (QALYs) are comparable over a patient's life-time (as per the lifetime perspective requested by the scope of this appraisal).

**Table 1: Total costs and QALYs of 3 alternative sequences containing 3 biologics**

| Standard of Care | DMARD-IR | TNF-IR | Post-rituximab |
|---|---|---|---|
| Etanercept<br>⇩<br>Rituximab<br><br>DMARDs<br>⇩ | *Tocilizumab*<br>⇩<br>Etanercept<br><br>Rituximab<br>⇩ | Etanercept<br>⇩<br>*Tocilizumab*<br><br>Rituximab<br>⇩ | Etanercept<br>⇩<br>Rituximab<br><br>*Tocilizumab*<br>⇩ |
| ⇩ | ⇩ | ⇩ | ⇩ |

| Palliative care | DMARDs<br><br>Palliative care | DMARDs<br><br>Palliative care | DMARDs<br><br>Palliative care |
|---|---|---|---|
| Total direct medical costs | **£95,464** | **£102,935** | **£97,402** |
| Total QALYs | **8.579** | **8.851** | **8.605** |

⇩ ⇩ ⇩ ⇩

The table above shows the position at which tocilizumab is actually added to the current treatment of care has limited impact upon the total costs and benefits over a patient's lifetime.

⇩ ⇩ ⇩

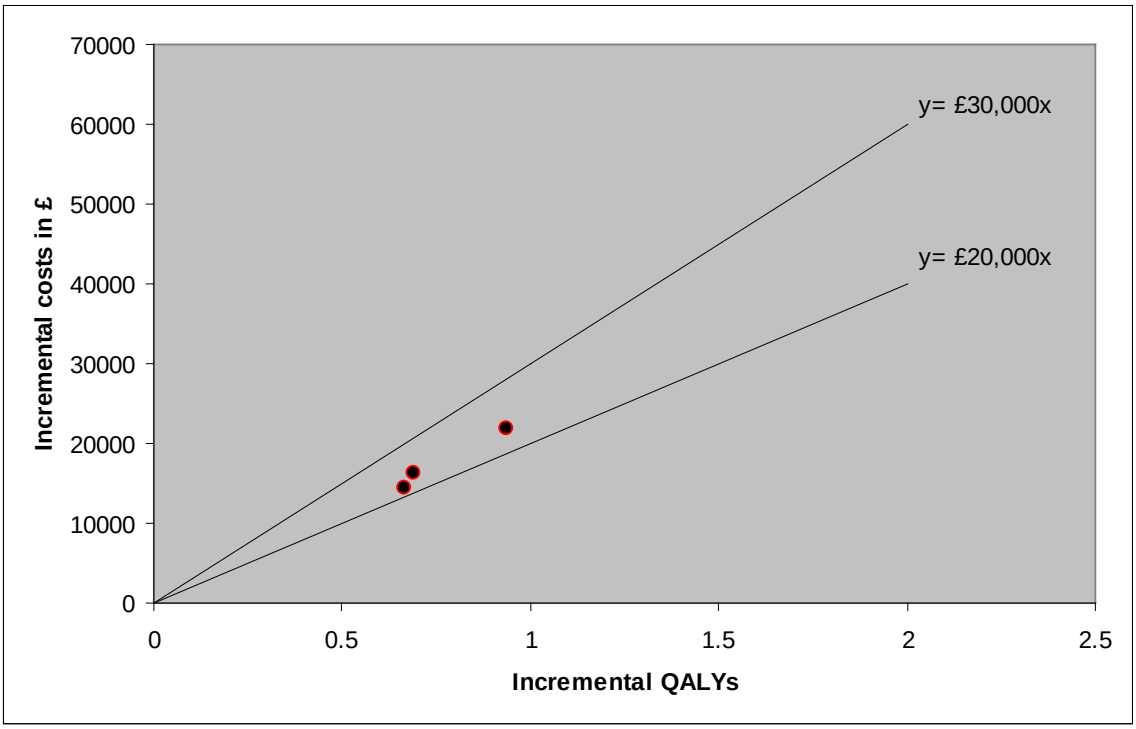
The differences in the total costs and benefits can be explained by uncertainty around the 'degradation' of ACR response rates (discussed below) when:

- etanercept is used after tocilizumab,
- rituximab is used after tocilizumab and etanercept
- tocilizumab is used after etanercept and rituximab.

Small differences can also be attributed to the discounting of costs and effects.

Overall the analysis shows that tocilizumab is a cost effective option as a treatment option for the treatment of RA. The ICERS of the 3 alternative biologic treatment strategies are £21,733 per QALY when tocilizumab is used in DMARD-IR, £23,409 per QALY in TNF-IR and £23,735 per QALY when tocilizumab is used after rituximab. Clinicians can therefore be given the autonomy to prescribe tocilizumab, an IL-6 inhibitor, reassured in the knowledge it is a cost effective strategy compared to existing standard of care.

**Figure 1: Cost effectiveness plane demonstrating that the 3 alternative treatment strategies**




It is important to note here that the 3 alternative biologic regimens all contain tocilizumab, therefore one is not answering the question of whether it is cost effective to add tocilizumab to the current standard of care.

Exploring the 'optimal' position of tocilizumab treatment lies outside the scope of this appraisal which states that the comparators should be "management strategies involving DMARDs without tocilizumab" it could also be argued this attempts to form a clinical guideline which lies outside the remit of the NICE STA process.

When considering the small differences and subsequent uncertainty when attempting to differentiate between the 3 tocilizumab strategies, this does not appear a major decision for the committee to be considering in the context of long term NHS costs and patient outcomes.

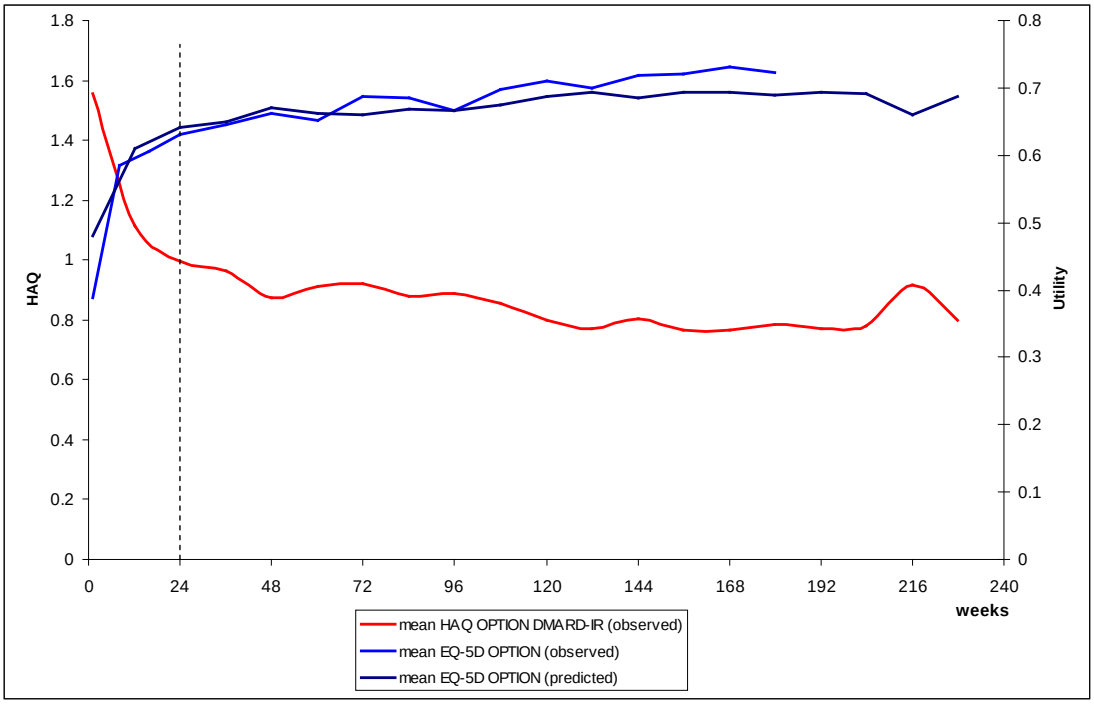
## 3 Updated cost effectiveness analysis accounting for the Committee's parameter recommendations demonstrates tocilizumab to be a cost effective treatment option when compared to existing standard of care

Roche has demonstrated that tocilizumab treatment offers an incremental benefit at an acceptable incremental cost when used at different positions in the treatment pathway of RA. Roche has explored scenarios, taking into consideration the Committee's suggestions, and updated the cost-effectiveness model. Revised cost effectiveness estimates of tocilizumab treatment when given in DMARD-IR, TNF-IR and rituximab intolerant, or unsuitable for, patients are presented in this response.

1. Roche has estimated that tocilizumab is a cost effective option for patients that are intolerant or unsuitable for treatment with rituximab. The incremental cost effectiveness ratio for the treatment with tocilizumab in this patient population is **£20,242 per QALY.**

2. Roche is submitting evidence that the long-term HAQ change while on treatment and the non-linear HAQ to EQ-5D utility mapping used in the tocilizumab original submission provides a robust estimation of the EQ-5D data observed in the trials, as shown in the figure below. Therefore the use of EQ-5D data directly within the model is unlikely to make any significant difference.

**Figure 2: Mean EQ-5D and HAQ observed in the OPTION trial overlaid with the predicted mean EQ-5D scores**



3. An attempt has been made to identify the best available data to evaluate the efficacy degradation of etanercept after the use of one biologic and efficacy data of rituximab after the use of 2 biologics. The economic case has been updated to reflect this "degradation" of response as requested by the committee. The updated ICERs are **£21,733 per QALY** and **£24,094 per QALY** for the DMARD-IR and TNF-IR respectively

4. Roche has performed the economic analysis using un-adjusted ACR response rates to account for the committee's reservations regarding the MTC. The updated ICER for DMARD-IR is **£23,339 per QALY**. However Roche still regards that the original MTC after accounting for the ERG criticisms offer the best available evidence base to inform the economic model in the DMARD-IR indication.

5. Roche is still unclear whether the Committee believes that palliative care is free of treatment related AEs and whether these have any impact upon patient quality of life. Clinical expert opinion to clarify the likely incidence of AEs in these late stages of the disease would be helpful.

Roche has re-estimated the cost-effectiveness analysis of tocilizumab taking into account the cumulative effect of all the changes in the model. The revised cost effectiveness estimates can be found in the table below.

**Table 2: Updated cost effectiveness analysis of tocilizumab in DMARD-IR and TNF-IR**

| | | **Tocilizumab model ACD 2** | Model assuming **reduction in efficacy** and **utilising unadjusted[+] tocilizumab response rates** |
|---|---|---|---|
| DMARD-IR | Incremental costs | £22,851 | £12,945 |
| | Incremental QALYs | 0.994 | 0.583 |
| | ICER | **£22,994 per QALY*** | **£22,175 per QALY** |
| TNF-IR | Incremental costs | £27,170 | £26,678 |
| | Incremental QALYs | 1.165 | 1.107 |
| | ICER | **£23,318 per QALY*** | **£24,094 per QALY** |

[+]*applies to DMARD-IR analysis only*

## 4 There are clear scenarios under which an IL-6 may be prescribed in preference to existing standard of care treatments in order to maximise patient benefit and therefore has a role to play in both the DMARD-IR and TNF-IR settings

Tocilizumab has demonstrated suppression of inflammation to all patients irrespective of the clinical manifestations and the different stages of the disease.

This is verified by the clinical trial results together with clinical expert opinion. These highlight the potential unique properties of an IL-6 inhibitor to patients with persistently high raised CRP, persistent or intermittent pyrexia of unknown origin assumed to be systemic inflammation after infection and neoplasia excluded, also patients with anaemia of chronic disease despite use of conventional DMARDs. Therefore despite other biologic options being available to clinicians within the DMARD IR and TNF IR settings, it is plausible that a clinician may consider an IL-6 inhibitor a more appropriate option to utilise in advance of other biologics.

We urge the committee to seek clinical expert opinion in order to determine under what conditions would clinicians utilise an IL-6 inhibitor in the future management of RA over the currently available biologic treatments.

## 1. DO YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT?

**1 Roche is seeking a recommendation for tocilizumab as *an option*, not as a permanent displacement of TNFs or rituximab. Clinicians should be allowed to position tocilizumab where they see fit within the treatment pathway as tocilizumab is cost effective in both the DMARD-IR and TNF-IR setting. Also the alternative tocilizumab positioning options does not significantly alter lifetime NHS costs and benefits**

In the original tocilizumab submission and responses during the ACD consultation periods Roche has attempted to answer whether adding tocilizumab in the treatment pathway and allowing clinicians to have the option to prescribe tocilizumab to patients that will receive maximum benefit from an IL-6 inhibitor is cost effective. By structuring the decision problem adding tocilizumab at the beginning of the treatment pathway Roche **is not seeking** guidance that will dictate the usage of tocilizumab before etanercept or rituximab but to evaluate the treatment within its licensed indications and consistent with the randomised controlled trials. By demonstrating that tocilizumab is cost effective and upon positive guidance from NICE, clinicians will have the opportunity to choose between the available treatments and prescribe first the treatment that will maximise patient benefit. Clinicians choosing to utilise the unique properties of one class of drugs to suppress the unique manifestations of the disease will preserve the other classes of drugs for a later stages once patients have had an inadequate response to the 1$^{st}$ treatment of choice.

If the management of RA included 3 biologic treatments the overall cost to the NHS would be approximately the same irrespective of the position that these treatments occupy in the treatment pathway, as demonstrated in the table below. Roche has explored 3 scenarios in which tocilizumab is added to the current treatment strategy. The DMARD-IR and TNF-IR scenarios represent the evidence base from the tocilizumab phase III trials.

It should be noted here that the 3$^{rd}$ scenario represents a position in the treatment algorithm in which tocilizumab's efficacy and safety has not been assessed nor demonstrated. The scenario is hypothetical and based on assumptions around tocilizumab's efficacy after patients have been treated with a b-cell depleting agent. It is provided here to demonstrate that the total costs and QALYs remain the same irrespective of the order of the 3 biologics.

**Table 3: Total costs and QALYs of 3 alternative sequences containing 3 biologics**

| Standard of Care | Post tDMARDs | Post TNF | Post rituximab |
|---|---|---|---|
| Etanercept<br>⇩ | *Tocilizumab*<br>⇩ | Etanercept<br>⇩ | Etanercept<br>⇩ |

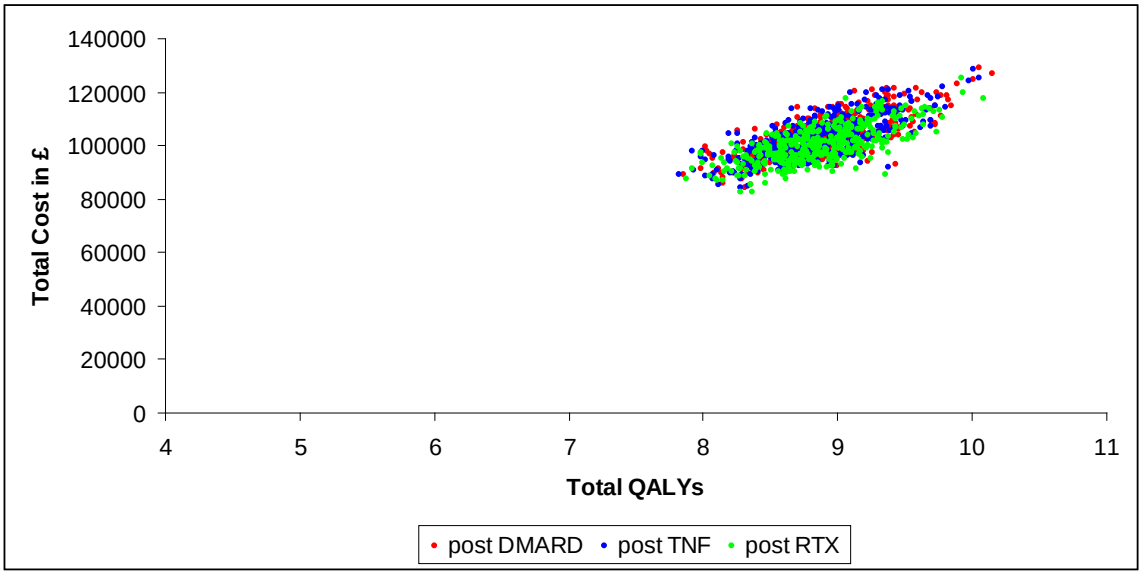
| | | | |
|---|---|---|---|
| Rituximab<br>DMARDs<br>⇩<br>Palliative care | Etanercept*<br>Rituximab*<br>⇩<br>DMARDs<br>Palliative care | *Tocilizumab*<br>Rituximab*<br>⇩<br>DMARDs<br>Palliative care | Rituximab<br>*Tocilizumab**<br>⇩<br>DMARDs<br>Palliative care |
| Total direct medical costs | **£95,464** | **£102,935** | **£97,402** |
| Total QALYs | **8.579** | **8.851** | **8.605** |

*Response rates degraded – see section below

As demonstrated in the table above the total costs and benefits that the 3 sequences offer are very similar. It should be noted here that differences in the total costs and QALYs between the 3 sequences can be attributed to discounting which affects the costs and benefits accumulated over a patient's lifetime in a different way depending on how the treatments are ordered, assumptions regarding tocilizumab's long-term efficacy when positioned after rituximab and etanercept plus assumptions with respect to 'degradation' of efficacy of biologics.

Uncertainty around the point estimates of the 3 scenarios was assessed with PSA. The results of the PSA are presented in the figure below. There is a considerable overlap between the 3 PSA 'clouds' which indicates very small differences between the 3 regimens.

**Figure 3: PSA results showing total life-time costs and QALYs for the three 3-biologic regimens**




It is important to note here that any cross regimen incremental analysis cannot be performed as this would lie outside the scope of this appraisal, as all regimens

contain tocilizumab, the intervention for this appraisal. It could also be argued that attempting to evaluate the optimum treatment sequence of RA biologics is the remit of a clinical guideline and not a single technology appraisal.

The objective of this analysis is to demonstrate that patient benefit can be maximised irrespective of the order of the biologics currently available in the NHS. Therefore clinicians should be able to prescribe tocilizumab according to its licensed indications, positioning it in the treatment algorithm depending on the patient characteristics and disease phenotype. The committee can take reassurance that this freedom of choice is permissible as tocilizumab can be demonstrated to be cost effective regardless of where it is utilised in the treatment pathway when compared to current standard of care.

## 2 Tocilizumab is a cost effective option for patients that are intolerant or unsuitable for treatment with rituximab

The decision problem in order to demonstrate tocilizumab's cost effectiveness within this specific setting is illustrated in the table below.

**Table 4: Decision problem for patients that are intolerant or unsuitable for treatment with rituximab**

| Current standard of treatment patients are intolerant or unsuitable for treatment with rituximab | Treatment strategy adding tocilizumab in the current standard of treatment |
|---|---|
| Leflunomide<br>⇩<br>Gold<br>⇩<br>Cyclosporine<br>⇩<br>Palliative care | Tocilizumab<br>⇩<br>Leflunomide<br>⇩<br>Gold<br>⇩<br>Cyclosporine<br>⇩<br>Palliative care |

It has been assumed that the patient population that will qualify for these treatment regimens is represented by the patient population found in the tocilizumab phase III RADIATE trial. Therefore for the purposes of the economic model it is assumed that the patient population has the same baseline characteristics and will exhibit the same benefits as demonstrated in the trial. The base case results for this population are shown in the table below.

**Table 5: Cost effectiveness results for patients that are intolerant or unsuitable for treatment with rituximab**

| | | Treatment sequence excluding tocilizumab | Treatment tocilizumab including |
|---|---|---|---|
| TNF-IR | Total costs | £44,216 | £72,228 |
| | Total QALYs | 4.397 | 5.780 |
| | ICER | **£20,242 per QALY** | |

**Revised model with updated rebound effect (back to baseline) assumption and updated admin cost*

As demonstrated above the ICER is well below the normally accepted NICE threshold confirming that tocilizumab is a cost effective option in this patient population.

## 3 Updated Economic model / ICER incorporating latest committee feedback

### 3.1 Treatments being less effective following other biologic use and how this can be implemented

Roche has considered the Committee's recommendations that in modelling the tocilizumab arm of the additive DMARD-IR scenario, etanercept is utilised after patients have shown an inadequate response to 1 biologic and rituximab is used after patients have responded inadequately to 2 biologics and as a result this may have an effect on patient response. Roche initially modelled these treatments with unchanged treatment efficacy based on the assumption the treatment effect is not affected by the multiple lines of biologics, since the 3 biologics belong to a different class of treatments and therefore affect different receptors/cells responsible for inflammation.

Roche however has taken into consideration the committee's recommendations and has calculated the cost effectiveness of tocilizumab applying a reduction in etanercept's and rituximab's efficacy if they followed tocilizumab in the DMARD IR and TNF IR settings respectively.

In the ongoing MTA the Assessment Group conducted a literature review on the efficacy of aTNFs post the failure of the 1$^{st}$ aTNF. The Group found that Karlsson (2008) reported ACR response rates for the aTNFs as a group. For rituximab 'degradation', the response rates were sourced from the REFLEX phase III study. A sub-group analysis of patients that had received and showed an inadequate response to more than one aTNF in the REFLEX trial reported ACR response rates for rituximab.

Additionally response rates for tocilizumab when given to patients that had an inadequate response to more than 1 aTNF were obtained from the RADIATE trial. A summary of all the 'degraded' response rates can be found in the table below.

**Table 6: Summary of ACR response rate evidence supporting the 'degradation' of response rates of biologics**

| | Tocilizumab utilised after 2 biologics | Etanercept utilised after 1 biologic | Rituximab used after 2 biologics |
|---|---|---|---|
| ACR 20 | 50.0% | 49.0% | 42% |
| ACR 50 | 30.8% | 25.8% | 22% |
| ACR 70 | 15.4% | 7.1% | 10% |
| Reference | ≥ 2 TNFs RADIATE trial (Emery et al. 2008) | Karlsson et al. (MTA assessment report) | ≥ 2 TNFs RADIATE trial analysis (Kremer et al. 2006) |

Utilising the above evidence Roche re-estimated the cost effectiveness of tocilizumab in both the DMARD-IR and TNF-IR indication.

**Table 7: Updated cost effectiveness analysis taking into account 'downgraded' ACR response rates for etanercept (after one biologic) based on the Karlsson data and rituximab based on the REFLEX data (after two biologics)**

| | | **Tocilizumab model ACD 2** | **Model assuming etanercept and rituximab reduction in efficacy** |
|---|---|---|---|
| DMARD-IR | Incremental costs | £22,851 | £14,454 |
| | Incremental QALYs | 0.994 | 0.665 |
| | ICER | **£22,994 per QALY*** | **£21,733 per QALY** |
| TNF-IR | Incremental costs | £26,640 | £26678 |
| | Incremental QALYs | 1.21 | 1.107 |
| | ICER | **£23,318 per QALY*** | **£24,095 per QALY** |

**Revised model with updated rebound effect (back to baseline) assumption, etanercept withdrawal rates, updated admin cost and revised pooled MTC estimates for etanercept*

The results of the analyses show that assuming a lowered efficacy has a marginal positive effect on the tocilizumab cost effectiveness in DMARD-IR. The results appear to be counter intuitive as lowering etanercept and rituximab ACR response rates in the tocilizumab containing arm lead to a reduction in the ICER. However this result can be explained as follows:

Examination of the results shows that the incremental benefit between the 2 treatment strategies has been lowered (as expected). Furthermore the incremental direct medical costs have also been reduced. This can be explained by the reduced response rates for etanercept and rituximab leading to a smaller proportion of patients remaining on these treatments post 6 months of treatment initiation. For example, etanercept has an ACR 20 of 62% in the non-tocilizumab arm (etanercept used as the 1$^{st}$ biologic). Data from Karlsson suggest that when etanercept is used as the 2$^{nd}$ biologic only 49% of the patients will achieve an ACR 20 and therefore continue receiving etanercept after the 1$^{st}$ 6 months.

3.2 Roche provide an analysis that addresses the Committee's concerns around the applicability of the tocilizumab long-term HAQ while confirming that the HAQ model predicts the EQ-5D data collected in the trials

In order to demonstrate that the cost effectiveness analysis is not biased in favour of tocilizumab when the mapping of HAQ to EQ-5D is utilised instead of the trial EQ-5D data, Roche is providing an analysis that attempts to validate the robustness of the non-linear mapping mechanism.

The analysis utilised the mean long-term HAQ data from the 2 trials (that collected both EQ-5D and HAQ; OPTION and LITHE) and the mapping mechanism to convert the observed HAQ scores into EQ-5D in the same way it is performed in the model in order to predict the mean EQ-5D scores over time.

The predicted utility scores from the HAQ mapping equation, are overlaid with the actual EQ-5D scores collected in each of the 2 trials to evaluate the differences between the predicted utility values and the observed utility values. As the chat below illustrates, the difference is very small.

In fact utilising the HAQ scores collected from the trial and the non-linear mapping mechanism appear to possibly underestimate utilities, therefore demonstrating that the Roche approach is conservative.

**Figure 4: Mean EQ-5D and HAQ observed in the OPTION trial overlaid with the predicted mean EQ-5D scores**

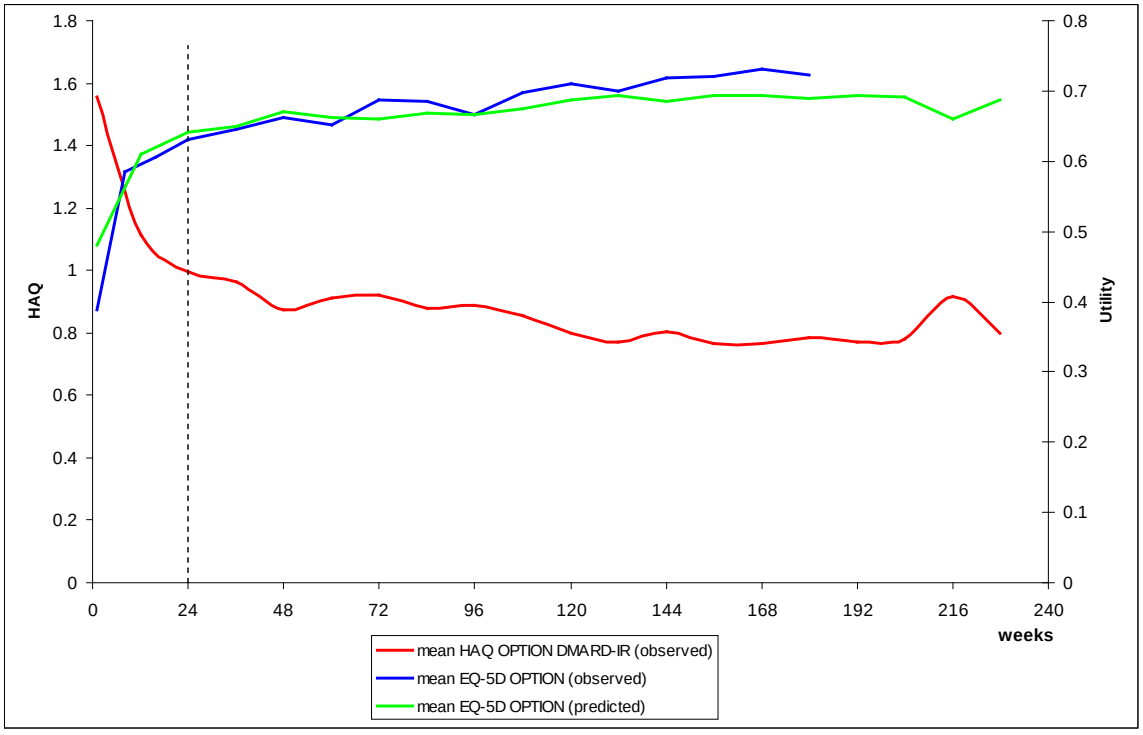
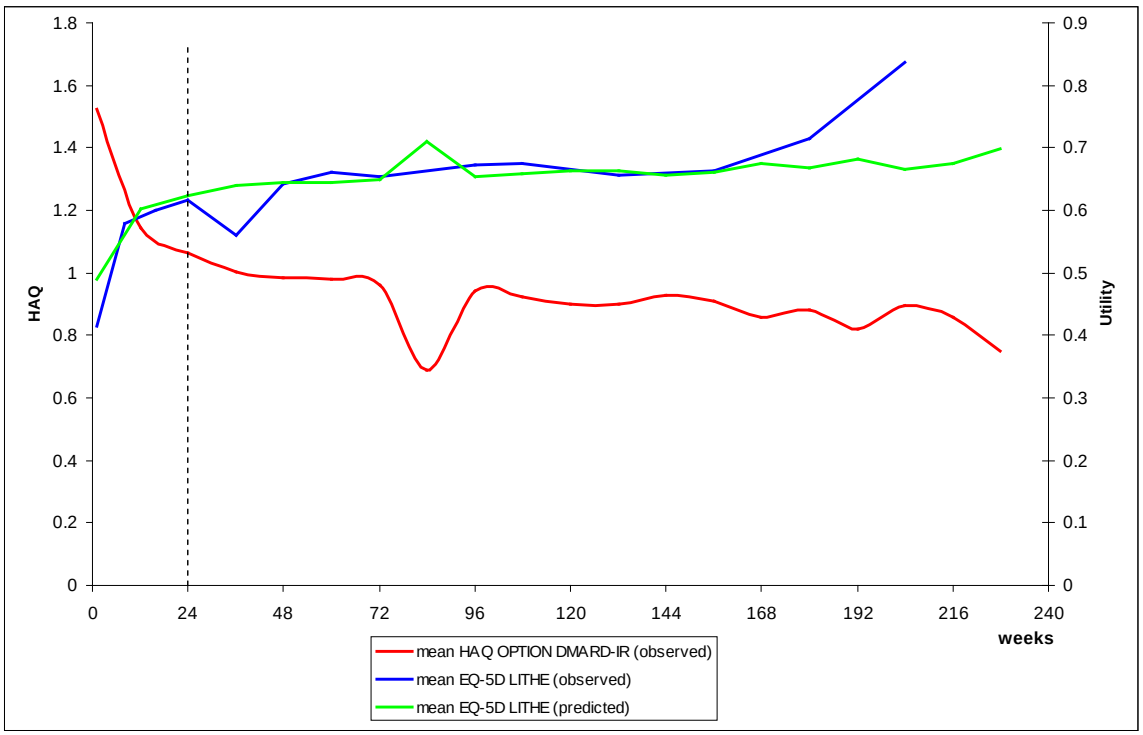


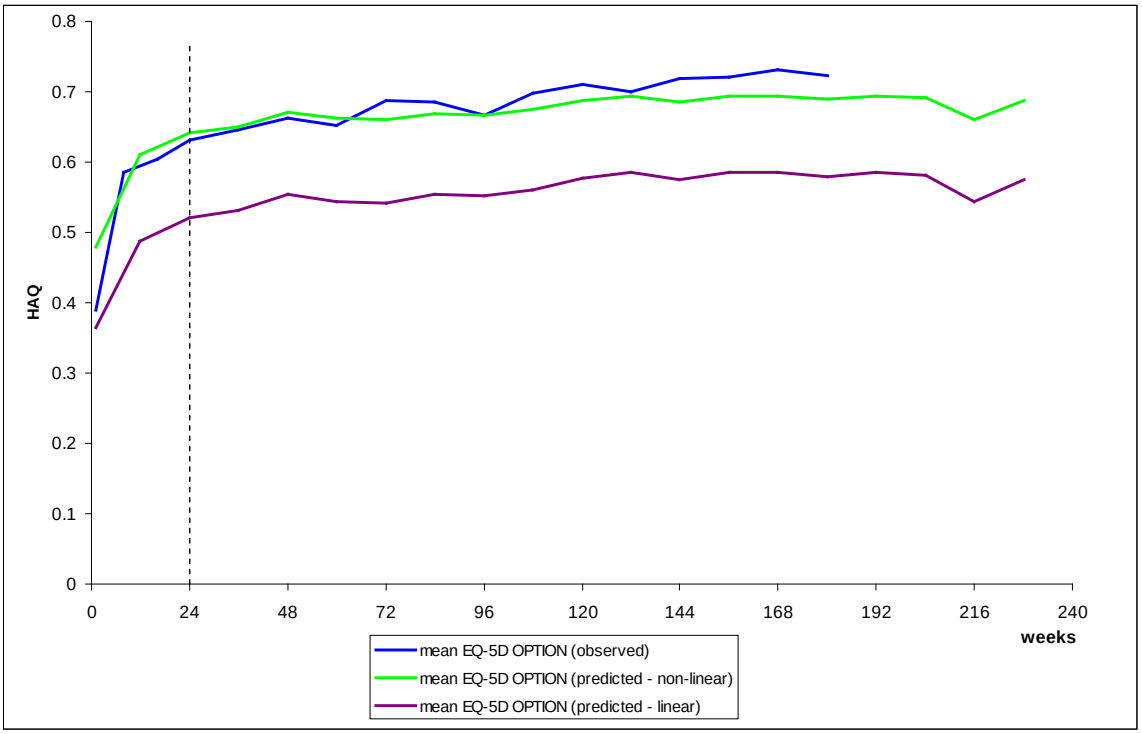
**Figure 5: Mean EQ-5D and HAQ observed in the LITHE trial overlaid with the predicted mean EQ-5D scores**




It can be seen above that there is longer follow-up for the HAQ data than there is for the EQ-5D data. However Roche is not extrapolating the long-term improvement of HAQ beyond week 168 in the DMARD-IR model and therefore is not biasing in favour of tocilizumab.

In order to validate that the non-linear mapping mechanism offers a better prediction than the linear mapping equation, Roche repeated the above analysis utilising the 2 different mechanisms. The results for the OPTION trial are presented below. The results for the LITHE trial data analysis can be found on appendix 1.

**Figure 6: Observed (blue) and predicted EQ-5D scores for the OPTION trial demonstrating the difference between the predicted values depending on the mapping mechanism utilised (purple - linear; green - non-linear)**




The predicted data in the figure above, derived using the two mapping mechanisms (Ducournau et al – green; Bansback et al – purple), demonstrates that converting HAQ scores to EQ-5D using a non-linear equation provides a superior fit to the observed data compared to the linear equation. A similar trend is observed in the LITHE analysis.

Roche is confident that the above analysis provides a validation of the approach taken in the submitted economic model. The model does not overestimate the long-term treatment effect of tocilizumab for responding patients but simply reflects what was observed in the trials. In addition, the predicted utility values generated from the non-linear mapping equation, as used in the Roche submission underlines the superiority of this mechanism compared to the linear mechanism previously used in the past appraisals of RA therapies.

It was not possible to replicate this validation exercise for the mean HAQ scores in TOWARD (DMARD-IR) and RADIATE (TNF-IR) as no utility data was collected as part of these trials.

Roche is committed to using the most appropriate parameters and analyses in the tocilizumab cost effectiveness model. Attempts have been made to address the Committees' request to evaluate a model that utilises the EQ-5D data directly from the 2 trials. However several major methodological limitations were encountered while developing the economic model and therefore Roche were

unable to construct a robust model within the ACD consultation period. The limitations included the following:

(i) EQ-5D data is only available for 2 out of the 3 DMARD-IR tocilizumab trials
(ii) EQ-5D data is not available from the TNF-IR indication - Collection of utility data was not part of the RADIATE trial protocol
(iii) Mortality of patients in the model depends on the relationship with HAQ score (Barton et al.) – see Roche original submission
(iv) Inpatient costs are calculated according to the patients HAQ score in the model – e.g. Patients with higher HAQ consume more healthcare resources (NORFOLK registry data)
(v) Long-term EQ-5D data for other treatments are not available e.g. evidence of palliative care disease progression only previously reported in terms of HAQ score.
(vi) An EQ-5D model would ignore the wealth of HAQ score data collected in all trials

## 2. DO YOU CONSIDER THAT THE SUMMARIES OF CLINICAL AND COST EFFECTIVENESS ARE REASONABLE INTERPRETATIONS OF THE EVIDENCE, AND THAT THE PRELIMINARY VIEWS ON THE RESOURCE IMPACT AND IMPLICATIONS FOR THE NHS ARE APPROPRIATE?

### 1 Why and when would a clinician utilise an IL-6 before a TNF-inhibitor

Whilst recognizing the need to increase the number of biologic therapies from two to three, the committee may not be aware of the heterogeneous population that makes up the rheumatoid arthritis population. This characteristic of the disease explains why there is still the need for an additional class of biologic, despite options already being available to clinicians within the DMARD IR and TNF IR setting. Unlike some other diseases, RA should be considered a mosaic of diseases all with a common phenotypical presentation in terms of swollen and tender joints. Variation occurs in terms of the different immunopathological drivers of the disease, that impact on both the severity and thus the treatment requirements of the patients This variation in disease manifestation, immunopathology, existing comorbidities, prognosis and subsequent impact on quality of life, results in a clinical need for varying therapies to be made available at all stages of the treatment algorithm, where licensed.

Tocilizumab has demonstrated suppression of inflammation to all patients irrespective of the clinical manifestations and the different stages of the disease. This is verified by the clinical trial results together with clinical expert opinion highlighting the potential unique properties of an IL-6 inhibitor to patients with persistently high raised CRP, persistent or intermittent pyrexia of unknown origin assumed to be systemic inflammation after infection and neoplasia excluded and patients with anaemia of chronic disease despite use of conventional DMARDs. Therefore despite other biologic options being available to clinicians within the DMARD IR and TNF IR settings, it is plausible that a clinician may consider an IL-6 inhibitor a more appropriate option to utilise in advance of other biologics.

### 2 The ACD does not accurately reflect or summarise all the data previously presented by Roche to the committee

The following section summarises 4 key issues where the ACD appears to not accurately reflect the evidence provided to date

2.1 <u>The committee is considering a limited time-horizon ignoring the life-time perspective required in modelling rheumatoid arthritis</u>

The committee has failed to consider tocilizumab according to the final scope of the appraisal by basing the decision not to recommend tocilizumab in DMARD-IR

and TNF-IR on a short-term time horizon. According to the final scope of this appraisal:

“The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes”.

Appropriately, in all past RA appraisals the time horizon used was that of a patient’s life-time.

Not recommending tocilizumab in DMARD-IR and TNF-IR on the basis of short-term additional cost perspectives associated with tocilizumab’s method of administration is limiting the scope of the appraisal to the first years of a patient’s life-time treatment strategy. This is clearly not in line with the final scope or NICE Guide to Methods. As illustrated in figure 3 above, the order in which the 3 biologics are prescribed makes very little material difference to lifetime costs and benefits.

## 2.2 ACR response rates and MTC

The NICE Guide to Methods in section 5.3.13 states the following: “*If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used*”.

Roche was committed to provide the most robust analysis in the original tocilizumab submission and therefore conducted a MTC to estimate the adjusted ACR response rates of tocilizumab and other biologics. Upon criticism by the ERG and the Committee, Roche revised the MTC to address these comments and excluded the Klareskog and Moreland trials. Roche submitted the revised MTC estimates as part of the response to the 2nd ACD. The results demonstrated that tocilizumab is as equally as effective as the aTNFs in DMARD-IR.

It is unclear to Roche why the committee has ignored the updated MTC analysis provided and instead suggest that etanercept “*may even dominate (that is, be more effective and less expensive) tocilizumab*“ (section 4.6 of the 3rd ACD) contradicting the analysis provided and recommend that the tocilizumab trial data are a “*more appropriate measure of the clinical efficacy*” (section 4.8 of the 3rd ACD) contradicting the spirit of the Guide to Methods.

However Roche has re-estimated the cost effectiveness of tocilizumab in DMARD-IR using the latest version of the model (submitted as part of the response to clarifications to the 2nd ACD) based upon the actual unadjusted trial ACR response rates for the treatments of interest. The results have a very minor effect on the ICER. The results can be found in the table below.

**Table 8: Cost effectiveness analysis using the unadjusted response rates**

| | | Tocilizumab model ACD 2 | Model utilising unadjusted ACR response for tocilizumab |
|---|---|---|---|
| DMARD-IR | Incremental costs | £22,851 | £21,374 |
| | Incremental QALYs | 0.994 | 0.916 |
| | ICER | **£22,994 per QALY*** | **£23,339 per QALY** |

**Revised model with updated rebound effect (back to baseline) assumption, etanercept withdrawal rates, updated admin cost and revised pooled MTC estimates for etanercept*

## 2.3 Use of HAQ and EQ-5D in the economic model

As part of the development of the economic model utilised in this appraisal, Roche conducted an extensive review of the published economic models and methods previously evaluated by NICE. Past RA models, developed both by manufacturers and Assessment Groups (BRAM), have consistently used HAQ as a surrogate outcome for patient quality of life. Roche replicated the published methods in the model submitted for tocilizumab. From the discussions that took place at the Committee meeting Roche believe that the Appraisal Committee still have some misunderstandings of the role of HAQ in the economic model. The following section attempts to re-clarify some important principles relating to this issue:

### Initial Response

A HAQ drop was derived according to a patient's ACR response category and 'no response' (derived from the tocilizumab trials).

When a patient in the model achieves a specific response (ACR 20, 50, 70, no response) a HAQ drop is applied to their baseline HAQ. This is the same for all treatments. For example, the same HAQ drop is applied to a patient achieving an ACR 20 on tocilizumab or on leflunomide and therefore tocilizumab is not favourably biased.

### HAQ change while on tocilizumab treatment (post first 6 months)

After the first 6 months that a patient is on treatment (and provided that the patient responded) a 'long-term' change of HAQ is applied in the model. Roche has demonstrated, by providing updates of the analysed data, that tocilizumab has a positive impact on HAQ while patients are on treatment.

On section 4.9 of the ACD the committee inaccurately noted "*there were very few people in the trial towards the end of the 3 year period on which the estimate of medium-term HAQ improvement was based*".

In the original submission Roche provided the mean HAQ trial data and patient numbers for both DMARD-IR and TNF-IR. Updates of the same data have followed, forming parts of the response to the 1st and 2nd ACD.

DMARD-IR (3-year follow-up):
Original submission (6/2/09) – 159 patients on tocilizumab
Response to 1st ACD (22/10/09) – 508 patients on tocilizumab
Response to 2nd ACD (20/1/10) – 888 patients on tocilizumab

TNF-IR (2.5-year follow-up):
Original submission (6/2/09) – 49 patients on tocilizumab
Response to 1st ACD (22/10/09) – 80 patients on tocilizumab
Response to 2nd ACD (20/1/10) – 96 patients on tocilizumab

Clearly the pooled DMARD-IR and TNF-IR extension trial follow-up data contain enough patients to derive meaningful trends of the long-term HAQ change while patients are on tocilizumab treatment.

In consideration of the comments made by the ERG and the Committee, Roche also addressed the "rebound effect" issue and modified the model so that patients that show an inadequate response to tocilizumab return back to their baseline HAQ. The modifications were introduced to the model as part of the response to the 1st ACD (22/10/09).

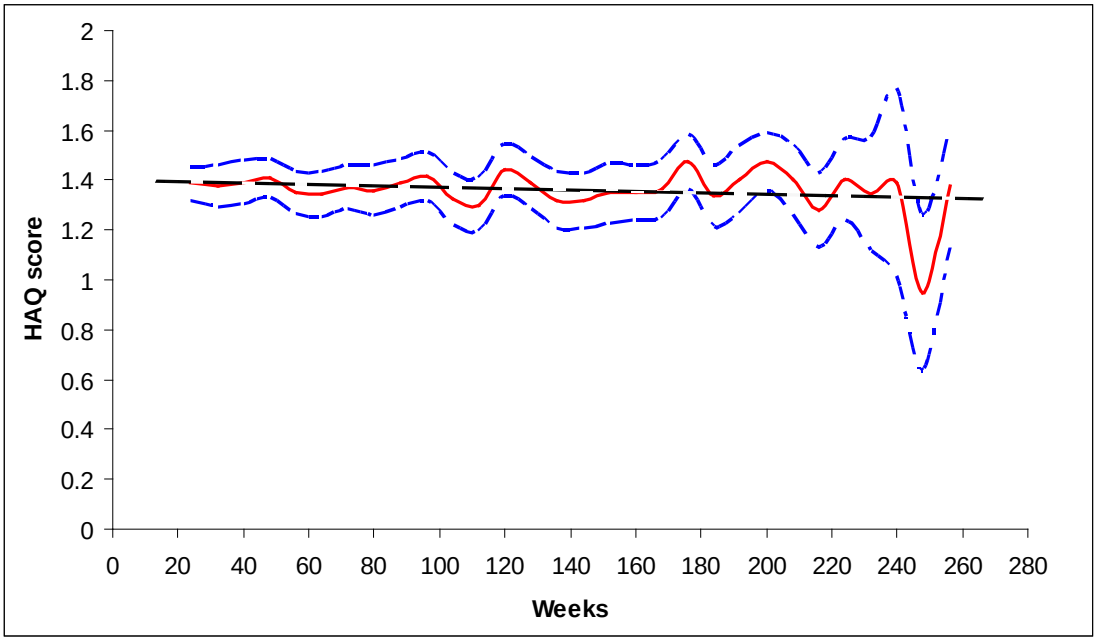
**HAQ change while on biologic treatment (post first 6 months)**

On section 4.9 the committee "*considered that it was unlikely that the medium-term HAQ progression with tocilizumab would be any different to other biologics, therefore the Committee dismissed the manufacturer's adjustments where tocilizumab was the only biologic that had a medium-term HAQ improvement.*"

The Appraisal Committee's considerations go against the available evidence base and submitted assumptions for the ongoing MTA of biologics used after the failure of an aTNF. Manufacturers of 2 aTNFs submitted an economic model that showed no improvement of HAQ while patients were on the respective treatment. In addition Roche submitted data from the rituximab extension trial showing that HAQ remained stable over time (Roche rituximab submission 10 August 2009). The results are reproduced in the figure below. Roche also ran a mixed model (same methodology that derived the tocilizumab HAQ change while on treatment) on the HAQ data and demonstrated that there is no HAQ change while patients

are on treatment (HAQ slope: 0.003 per cycle; p-value > 0.05; not statistically significant).

**Figure 7: Long term HAQ change for rituximab patients remaining on therapy (REFLEX extension population)**




Given the above evidence it is clear that the positive effect on HAQ is uniquely demonstrated when patients are tocilizumab treatment and that the committee is ignoring important clinical evidence based on the premise that all biologic RA treatments should be/are exhibiting the same effects.

## Incorrect conclusions around HAQ and EQ-5D mapping

On section 4.11 of the 3rd ACD the Committee "*was concerned that the HAQ mapping appeared more favourable to tocilizumab than the directly observed EQ-5D data. In addition, the use of mapping resulted in negative utilities that represented states worse than death*".

Roche demonstrated in section 3.2 above that the concerns are unfounded and that the non-linear mapping mechanism is robust. In addition, as part of the response to the 1st ACD, Roche (response dated 22/10/09; Appendix II) provided the underlying data used in the derivation of the mapping mechanism. These show that a subset of the utility values observed in the trials were indeed negative (n = 797). Furthermore the EQ-5D data collected in the LITHE and OPTION trials show that the patients' utility values span the whole range of utility (response dated 22/10/09; Appendix II).

Based on data already submitted to NICE and the shortcomings of the EQ-5D approach and the independent review conducted by Birmingham University as

part of the ongoing MTA, Roche believe that mapping of HAQ to EQ-5D is necessary in order to fully capture the HRQoL of patients.

2.4 The evidence base for the Appraisal Committee's position on Adverse Events is unclear and does not reflect the most recent analysis presented by Roche

In section 4.12 of the 3rd ACD "*The committee concluded that the effects on health-related quality of life and the costs of treating adverse events associated with tocilizumab should have been incorporated into the economic model and that the ICER could increase substantially*".

Roche is unclear what the analysis was and how it contributed to the Committee's conclusion regarding AEs. 2 separate analyses have been presented to the Committee with respect to the impact of AEs to HRQoL. This has a major impact on the ICER and it is therefore critical that a transparent assumption and corresponding justification is provided.

(a) The ERG presented an analysis in the 1st Committee meeting that included a 0.05 disutility for every cycle of the model excluding palliative care

(b) Roche presented a similar analysis to the ERG as part of the response to the 1st ACD (22/10/09) that included in the economic model a 0.05 disutility for every cycle including palliative care

There is a consensus between the 2 analyses to include a disutility decrement for the cycles patients spend on tocilizumab, other biologics and DMARDs. The difference between the two models is introduced around the uncertainty of the inclusion of AE disutilities in palliative care and not around the inclusion of AE disutilities for tocilizumab. The Committee with the assistance of clinical expert opinion requires further insight into the typical AEs associated with palliative care in RA. The ERG method assumes that treatment with glucocorticoids, analgesics, cytotoxics and unlicensed immunosuppresants in this late stage of disease is adverse event free.

Roche after carefully reviewing all the available evidence (Roche response to 2nd ACD) suggests a more reasonable assumption is that any disutility applied in the model should also be applied in the cycles that patients spend on palliative care.

It could also be argued that any disutility associated to treatment related AEs has been captured in the EQ-5D utility data collected in the tocilizumab phase III trials. Roche has demonstrated that mapping from HAQ to EQ-5D predicts the observed utility values with precision and therefore the mechanism captured any disutility related to adverse events.

## 3. DO YOU CONSIDER THAT THE PROVISIONAL RECOMMENDATIONS OF THE APPRAISAL COMMITTEE ARE SOUND AND CONSTITUTE A SUITABLE BASIS FOR THE PREPARATION OF GUIDANCE TO THE NHS?

The 3rd ACD is not a suitable basis for the preparation of guidance for the reasons outlined in sections 1 and 2 above. In summary, tocilizumab has been demonstrated to be cost effective within its licensed indications compared to the existing standard of care. Therefore whether a clinician chooses to prescribe tocilizumab in the DMARD IR or TNF IR setting, the committee can be reassured it is a cost effective treatment strategy.

The apparent desire of the committee to suggest where in the RA treatment pathway tocilizumab should be positioned is inappropriate for 2 key reasons.

Firstly this appears an exercise more consistent with an RA clinical guideline and not consistent with an STA with a final scope that states explicitly the relevant comparator and intervention are treatment strategies with and without tocilizumab.

***Final scope***
Intervention: Tocilizumab alone or in combination with methotrexate
Comparators: Management strategies involving DMARDs without tocilizumab

Secondly even if such attempts by the committee are considered appropriate within the context of an STA, this could be considered of limited value. The reason being the order in which the 3 available biologics are prescribed makes an insignificant difference to the lifetime NHS costs and patient benefits. It therefore does not appear a worthwhile use of committee time to attempt to differentiate between such poorly differentiated treatment strategies.

## 4. ARE THERE ANY EQUALITY RELATED ISSUES THAT NEED SPECIAL CONSIDERATION THAT ARE NOT COVERED IN THE ACD?

None

## References

Karlsson JA, Kristensen LE, Kapetanovic MC, Gulfe A, Saxne T, Geborek P. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology 2008; 47(4):507-513.

## Appendix 1

**Figure 8: Observed (blue) and predicted EQ-5D scores for the LITHE trial demonstrating the difference between the predicted values depending on the mapping mechanism utilised (purple - linear; green - non-linear)**