[redacted]

Thursday 20th January 2010

Laura Malone
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

BY E-MAIL

Dear Laura,

SINGLE TECHNOLOGY APPRAISAL – Tocilizumab for the treatment of rheumatoid arthritis

Thank you for sending us the 2nd Appraisal Consultation Document (ACD) for the tocilizumab single technology appraisal. Roche is disappointed that the Appraisal Committee has not recommended tocilizumab when evaluating the available clinical and cost effectiveness evidence.

In response to the additional economic analysis requested by the committee in section 1.2, Roche's response to these requests is summarised in Table 1 below.

In relation to the additional data requested within the ACD, Roche has provided these under section 1 of our response below. The new data provided includes:

i) Updated long-term tocilizumab HAQ data
ii) EQ-5D data from the LITHE trial
iii) Safety data from the Japanese surveillance study

Table 1: Rationale for the inclusion or exclusion from the Roche analysis and updated cost effectiveness results in DMARD-IR and TNF-IR

	Description	Updated ICER	Rationale for inclusion/exclusion
Scenario 1	Tocilizumab as a **replacement** therapy to the anti-TNFs	Not provided	**Excluded:** – Exceeds remit of STA as assumes permanent replacement of anti-TNFs on the NHS – Excludes evaluation of treatment strategy with largest clinical benefit
Scenario 2	Tocilizumab as an **additive** therapy in DMARD-IR	£23,655 per QALY	**Included:** – Addresses large unmet need through evaluating advancement of the management of RA from 2 classes to 3 classes of biologics
Scenario 3	Tocilizumab as a **replacement** therapy to rituximab	Not provided	**Excluded:** – Exceeds remit of STA as assumes permanent replacement of anti-TNFs on the NHS – Excludes evaluation of treatment strategy with largest clinical benefit
Scenario 4	Tocilizumab as an **additive** therapy in TNF-IR	£23,318 per QALY	**Included:** – Addresses large unmet need through evaluating advancement of the management of RA from 2 classes to 3 classes of biologics
Scenario 5	Tocilizumab as a therapy for rituximab inadequate responders (RTX-IR)	Not provided	**Excluded:** – Clinical and safety tocilizumab data unavailable

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

Yours Sincerely,

EXECUTIVE SUMMARY

1. NICE have been inconsistent in the application of the methodology and assumptions used to evaluate tocilizumab compared to previous and recent technology appraisals of RA biologics

NICE is appraising tocilizumab by applying a different approach and an alternative set of modelling assumptions compared to all previous RA appraisals. Roche believe that this is unfair given NICE's and the ERG's experience with assessing therapies for the treatment and management of RA. The main points of inconsistency are summarised in the table below.

Table 1: Comparison of parameters and approach used by NICE and the ERG in past and recent RA appraisals and the tocilizumab appraisal

Methodology/Approach	NICE/ERG approach in tocilizumab appraisal	NICE/ERG approach in TA36, TA130, TA141 and ongoing MTA
Additive vs replacement approach to the decision problem	Recommendation partially based on **replacement approach** to the decision problem	Positive recommendations based on **additive approach**
Average patient weight	Request for calculation of annual cost base on a **75kg** patient	Calculation of annual cost for IV therapies base on a **70kg** patient
Administration cost	**£203 per administration**	**£124** (early appraisals) inflated to £**142 per administration** (ongoing MTA)
Inclusion of AEs cost and disutilities	Request to **include** cost and disutilities	Cost and disutilities **excluded**
HAQ-utility mapping	**Linear mapping**	**Non-linear mapping (recent MTA)**
ICERs	**Not recommended:** ICER: £32K per QALY (DMARD-IR)	**Recommended:** ICERs: £28K - £46K per QALY (TA 130; DMARD-IR)

Roche is unclear why NICE is basing its provisional recommendation for tocilizumab on these significantly different set of assumptions and approach. For all alternative assumptions currently selected by NICE, the ICER increases..

2. The suggested economic model inputs within section 1.1 of the ACD are unreasonable in light of the available evidence and the spirit of the NICE Guide to Methods. Selecting parameters based upon the best available evidence generates an ICER for tocilizumab below the NICE threshold for both the DMARD IR and TNF IR populations

Table 2: Summary of economic model refinements and revised Roche cost effectiveness estimates

Model Assumption	Roche revised model – 2nd ACD – ICER – DMARD-IR	Roche revised model – 2nd ACD – ICER – TNF-IR
Roche base case	£19,870 per QALY	£22,003 per QALY
Using un-pooled MTC estimates	£20,250 per QALY	N/A
Withdrawal rate of etanercept used	£20,166 per QALY	N/A
Negative (3 years in DMARD-IR; 2.5 years in TNF-IR) and rebound effect (Back to baseline)	£22,003 per QALY	£22,876 per QALY
AE utility decrement equal to 0.05 per cycle	No Change	No Change
Administration cost equal to £154.3	£20,334 per QALY	£22,428 per QALY
Exponential long-tem HAQ modelling	£18,704	£19,478
Cumulative Impact of Changes	**£23,655 per QALY**	**£23,318 per QALY**

The committee has failed to acknowledge further analysis of key parameters of the economic model undertaken by Roche as part of the response to the 1st ACD. In light of new evidence made available from the tocilizumab trials but also from the analysis undertaken by Birmingham University and published in the MTA Assessment Group report for “Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor” Roche has revised key parameters affecting both the evaluation of the DMARD-IR and TNF-IR indications. The 5 key parameters are discussed in Section 2 and are summarised as follows:

1. Inclusion of adverse event disutilities and costs

It is unrealistic and unreasonable for NICE to request from Roche to provide and include robust AE cost and disutilities for all treatments included in the economics model. Firstly it is not possible to generate the necessary data within the time that Roche had to respond to this consultation and secondly the historical precedents set by positive recommendations published for RA in the absence of such data.

Given the nature of the disease, patients are exposed to treatment from the point of initial diagnosis. After conducting a literature review and consulting with clinical experts Roche believes that disutilities and treatment costs associated with adverse events relating to the patient exposure to bDMARDs are less than or equal to those associated with therapy in the later stages of the disease (palliative care). Continuous exposure to glucocorticoids and analgesics plus the potential addition of cytotoxics and unlicensed immunosuppresants in palliative care can have detrimental effects to patients' health, QoL and have high associated costs of treatment. Failure to account for adverse events relating to all lifetime therapies would bias any ICER against the additive therapy.

Therefore Roche has included the ERG recommended arbitrary utility decrement for all cycles for which patients receive treatment including palliative care. Under these conditions, the base case ICER remains unchanged in both the DMARD-IR and TNF-IR indications.

2. HAQ to utility mapping

In light of the new analysis produced by Birmingham University as part of the recently published MTA Assessment Group report, Roche is confident that the tocilizumab derived mapping is a robust approximation of the relationship between HAQ and utility.

After the independent review and analysis that Birmingham University conducted, it was found that mapping of HAQ on QoL follows a quadratic function similar to Roche's findings.

When Roche used the Birmingham derived mapping mechanism the cost effectiveness of DMARD-IR base case analysis changed from £19,870 per QALY to £19,685 per QALY and the TNF-IR changed from £22,003 per QALY to £22,523 per QALY.

3. Long-term HAQ data

It is unjustifiable to dismiss phase III tocilizumab data on the grounds that no other treatment has exhibited such results. Within the context of how this data is applied within the economic model, the fact the data is not comparative to anti-TNFs is not a significant issue. Taking an additive approach, the anti-TNFs appear in both arms of the economic model, therefore the comparative efficacy of tocilizumab and anti-TNFs is not required.

Roche is not attempting to assert the superiority of tocilizumab over other bDMARDs but is following good modelling practice, as recommended by NICE, and using all available evidence to inform this parameter estimate.

It is important to note that Roche is utilising trial data which shows a statistically significant trend. This trend has remained stable and significant, as additional data

have become available after our initial submission. Roche assumes that the negative slope only applies for the duration for which it is observed in the trial. For patients that remain in the model past this point we assume a flat slope. The result is that a large proportion of responding patients remain in the model past this point but no benefit relating to a negative HAQ slope is assumed.

As a sensitivity analysis, Roche introduced a negative slope for all bDMARDs in the model. The resulting ICERs changed from £19,870 per QALY to £25,458 per QALY and the TNF-IR changed from £22,003 per QALY to £24,237 per QALY.

4. Weight based costing

The committee requested Roche to include in its analysis the cost of tocilizumab calculated on a weight figure derived by a consultee, despite the absence of documentation and a lack of public scrutiny. Moreover evidence published in a previous RA appraisal quoting the same source has referenced a significantly different figure. Roche believes that the best way to calculate tocilizumab's annual cost is by utilising the phase III trial data to which its efficacy is inherently linked. This allows for the accurate accounting of wastage, the distribution of patient weight and missed doses, as illustrated in Roche's original submission

The average weight on which the annual cost is based is 70 kg. The same figure has also been reported and used in the calculation of cost effectiveness in all past RA appraisals (TA130, TA126, and TA141) and recent MTA Assessment Group report. Therefore using a different average weight, to calculate the average annual cost is posing an inequity compared to past RA appraisals.

5. Administration cost

Roche believe that the administration cost derived from past RA appraisals and inflated to reflect cost in 2008 is a robust approximation of the opportunity cost to the NHS. The evidence provided by the clinical experts in the 1st committee meeting and a time-and-motion study conducted by Roche suggest that tocilizumab is administered without complications over the period of 1 hour. Therefore costing the administration for a half-day infusion is an overestimation of the true cost to deliver tocilizumab.

The probabilistic sensitivity analysis conducted as part of the original submission and response to the first ACD included the administration cost of tocilizumab as a variable. Therefore the range suggested by the committee has been taken into account when Roche and the ERG considered the uncertainty around the cost effectiveness point estimates in both indications.

3. IL-6 inhibition represents the introduction of a new mechanism of action and new class of biologic therapy in the management of RA. Failure to select the most appropriate decision problem fails to adequately evaluate the benefit and innovation such a treatment may add to the lifetime management of RA.

Selection the most relevant scenarios for the purposes of cost effectiveness analysis

Roche's original submission attempted to answer whether adding tocilizumab in the current RA treatment strategy was a cost effective option for the treatment of RA. Roche believes that the improvement of the life-long management of RA patients can only advance at this point in time if the current treatment strategy moves from utilising 2 biologics targeting 2 distinct inflammation factors to utilising 3 biologics targeting 3 distinct inflammation factors. This is best reflected in the additive **scenarios 2 and 4**. Therefore, in this response, Roche will focus on addressing these 2 scenarios.

Scenario 5 is also of relevance to the NHS but more clinical research is required, as tocilizumab has not undergone a clinical trials program in this patient population.

Roche does not include analysis for **scenarios 1 and 3**, as these are inappropriate to evaluate the adoption of a new class of drugs by the NHS. These scenarios assume TNF inhibitors and rituximab respectively would not be utilised in future NHS practice if tocilizumab were recommended by NICE. Given the implausibility of this scenario they are of no practical relevance to the scenarios faced by the NHS.

Adoption of such a replacement strategy would, in this or future RA appraisals permanently leave the management of the disease with 2 biologic treatments, therefore leaving patients exposed to palliative management of the underlying disease progression and symptoms for an extended period of time.

Selection of the most appropriate scenarios for the future management of Rheumatoid Arthritis

The current ACD through endorsing a replacement strategy for tocilizumab fails to understand rheumatoid arthritis as a syndrome with high unmet need, but appears to treats it rather as an acute episode.

RA has a remarkable variety of phenotypic and biologic variation. It should therefore be considered a mosaic of diseases under the single historical classification of rheumatoid arthritis. Historically, this classification was based on the similar presenting signs and symptoms, which were largely articular in origin. It is however now known that there are different sub types of RA that are unique in terms of their immunological drivers that results in both the classical articular manifestation of the disease but also the systemic manifestations that range from sub-cutaneous nodules to destructive lung and cardiovascular disease. Thus the Appraisal Committee needs to assess therapies with this understanding of the disease. It is well documented that patients respond to different treatments in different ways and with various levels of

success therefore creating a high unmet need alternative ways (modes of action) to control the inflammatory cascade.

The consideration by the Appraisal Committee of the appropriate use of a new class of biologics, such as tocilizumab an IL-6 inhibitor, in the chronic management of RA is not reflected in the ACD. When applying scenarios 1 and 3, the life-long management of RA will not advance. NICE is partly forming its negative recommendation for tocilizumab on the perverse assumption that new treatments will replace already existing and widely used treatments without considering that already existing and new innovative treatments can be used sequentially in the NHS. NICE and the Appraisal Committee need to re-evaluate the fundamental assumptions around the decision problem and answer the question of the most interest to patients and the NHS.

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

1. **According to the NICE Guide to Methods for Technology Appraisals and evidence based decision-making, it is unclear why NICE prefers to use an assumption instead of the long term HAQ data from the tocilizumab trials. Provision of the latest tocilizumab clinical data (below) provides even greater follow-up than earlier reports submitted to NICE and remains completely consistent with previous analyses: a significant downward trend in HAQ score is associated with patients who remain on tocilizumab treatment.**

Roche has provided NICE and the ERG with the most recent cut of the long-term tocilizumab HAQ data (November 2009) to support the robustness of the data and evidence based modelling approach.

Tocilizumab has demonstrated that it has a continuous effect on a patient's HAQ score in both DMARD-IR and TNF-IR populations. After the HAQ data update provided in October 2009 (1st ACD) Roche has re-estimated based on the November 2009 cut-off the long-term HAQ change while patients are on tocilizumab treatment. The updated HAQ slopes have been estimated to be -0.0144 and -0.0126 for DMARD-IR and TNF-IR respectively (per 6 month cycle; using the mixed model methodology used in the original submission). The clinical data used to estimate the updated slopes are shown in Figure 1 and Figure 2. Roche recognised in the original submission that the data beyond week 156 (3 years; DMARD-IR) and week 132 (2.5 years; TNF-IR) were based on limited patient numbers and therefore did not extrapolate tocilizumab's benefit beyond that point. This is a very conservative approach in light of the new evidence demonstrating that the long-term improvement for patients remaining on therapy, is observed for more than 3 years in DMARD-IR and 2.5 years in TNF-IR populations.

Figure 1: Mean HAQ score over time for patients in the pooled DMARD-IR trials (November 2009 update)

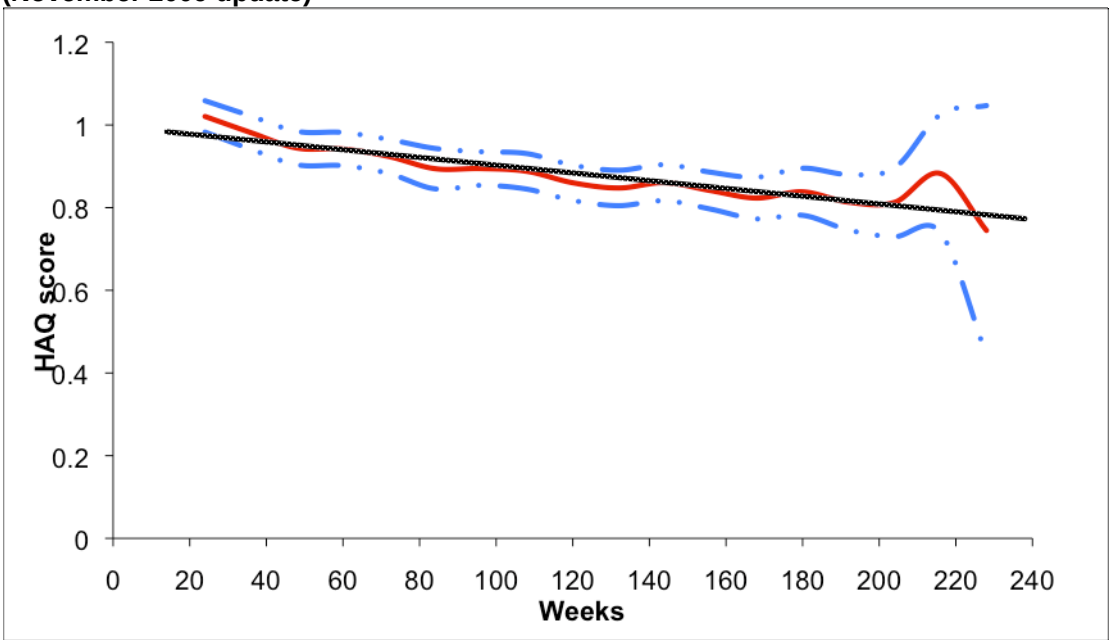
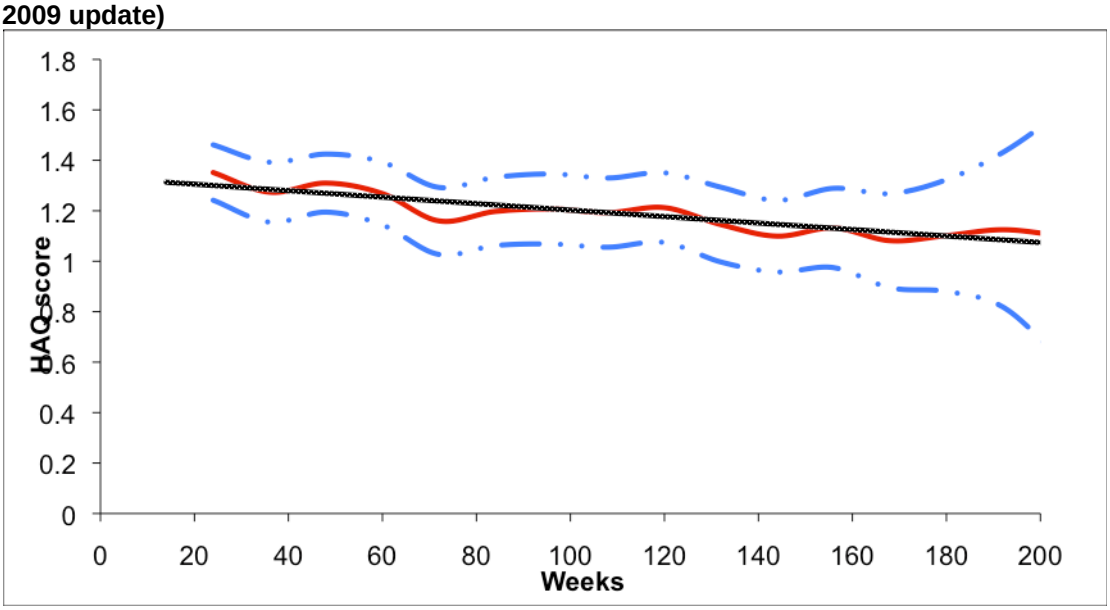


Figure 2: Mean HAQ score over time for patients in the pooled TNF-IR trial (November 2009 update)

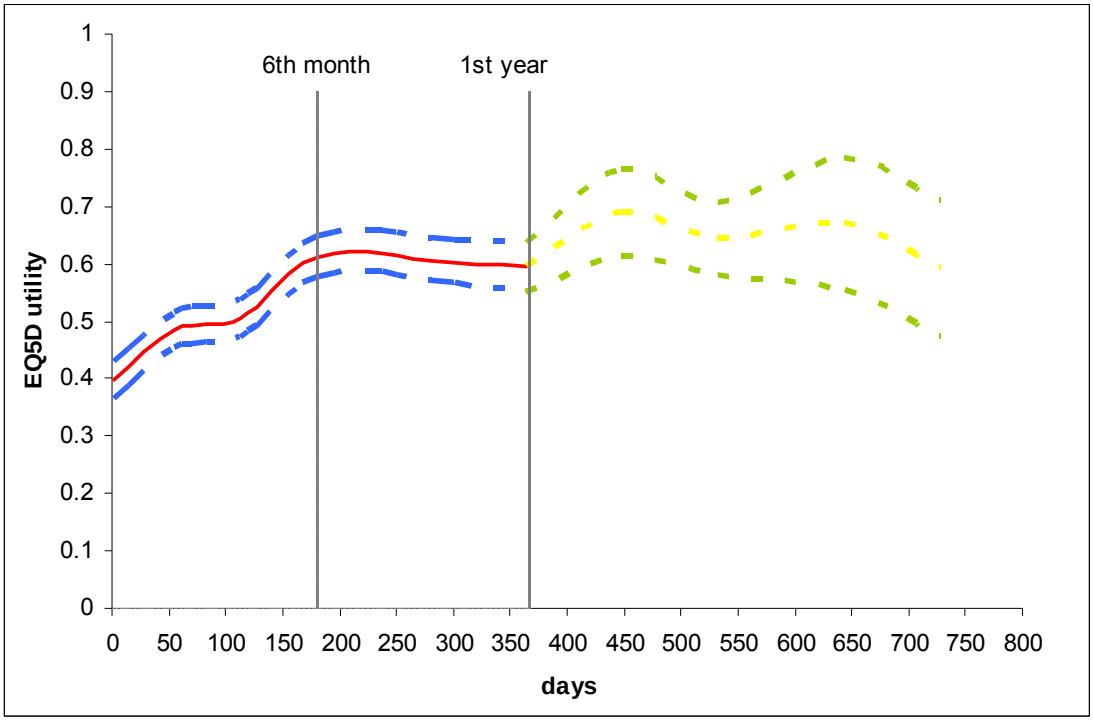


Patient numbers, means and CIs can be found in Appendix I.

2. Long-term EQ-5D (by treatment arm) from the LITHE trial as requested within the ACD

As requested in section 1.2 of the ACD, Roche is providing below the long-term EQ-5D data by arm from the LITHE phase III RCT. Long-term EQ-5D data from the OPTION phase III trial are only available for the tocilizumab arm and were provided as part of the original submission. A further update was provided as part of Roche's response to the 1st ACD.

Figure 3: Placebo + MTX long-term EQ-5D data from LITHE phase III RCT



According to the trial protocol, patients that did not respond to placebo + MTX by week 16 were allowed to escape to tocilizumab treatment. Responding patients that exhibited a 70% reduction in swollen and tender joints and completed year 1 were permitted to remain on double-blind placebo treatment (LITHE trial protocol). This is depicted in the figure above by the yellow line. 34 positive selected patients remained on placebo treatment at the end of year 1; 21 patients (19 valid EQ5D observations) completed year 2. The low patient numbers are reflected by the wide CIs. When considering the importance of this data in the context of estimating the tocilizumab ICER the following points are of high importance:

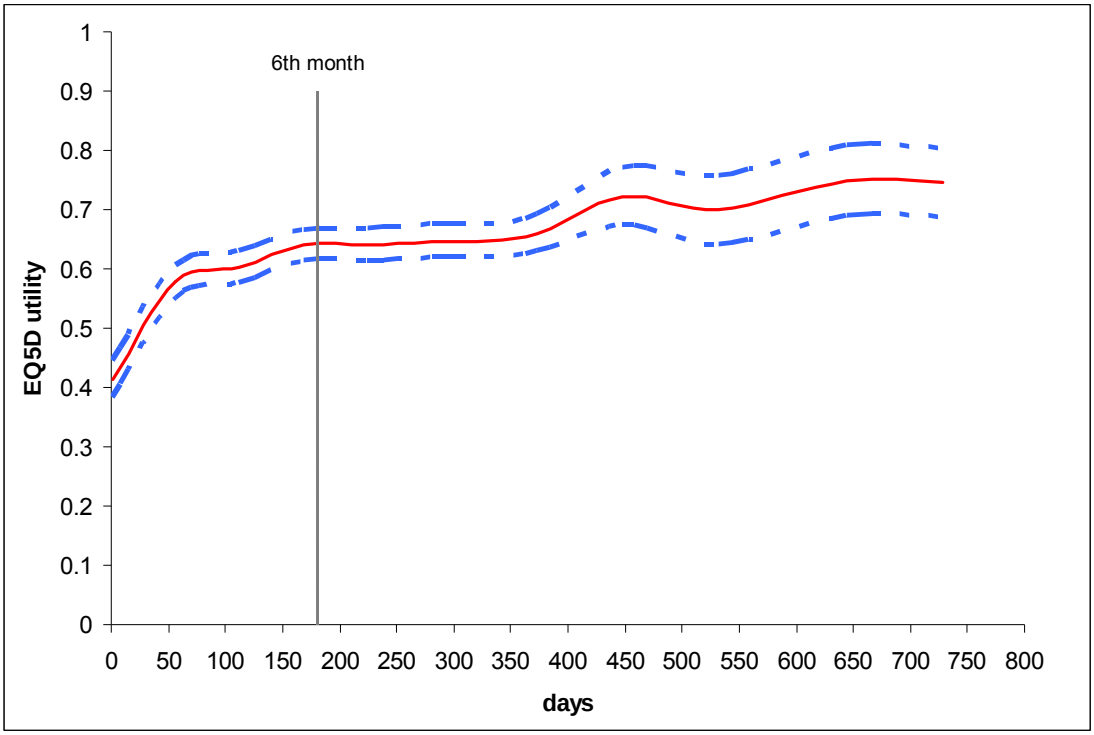
a) The fact these very select strong responders to MTX in the DMARD-IR setting have an increase in utility score in the first 6 months is not surprising. The analysis fails to account for the important fact that a far greater proportion of patients receiving tocilizumab achieve such high levels of response.

b) A positive utility impact (HAQ improvement) over the first 6 months is assumed for all responding patients in the model regardless of treatment. The utility trend over time (post the 6^{th} month) of the 21 patients receiving placebo + MTX treatment is unlikely to be observed in the very late stages of the disease where the long term HAQ of MTX are actually applied in the economic model.

c) The impact of assuming a negative HAQ slope for other treatments within the DMARD-IR setting has been evaluated in section 3 (paragraph 2.3) below and illustrates this assumption does not have a large influence on the tocilizumab ICER as they appear in both arms of the model (section 2.2 below)

d) Making any comparative efficacy claims between tocilizumab and MTX based upon figure 2 and 3 is highly flawed. Firstly the data is not randomised. Secondly the effectiveness of an RA therapy can not be measured on the HAQ instrument alone. Finally the curves take no account as to the number of patients receiving tocilizumab and MTX who achieve such a high response. The economic model utilises the respective ACR response data to account for these proportions.

Figure 4: Tocilizumab 8mg + MTX long-term EQ-5D data from LITHE phase III RCT



In the figure above it can be seen that EQ-5D utility is continuously increasing over time for patients that receive tocilizumab treatment. The positive trend is sustained post the 1st year follow-up suggesting that QoL improves over time in this heterogeneous population (ACR20, 50 and 70 patients).

Patient numbers, means and CIs can be found in Appendix II.

3. Results from the Japanese post-marketing trials as requested within the ACD demonstrate that no new safety signals have emerged with prolonged exposure to tocilizumab supporting the a favourable benefit/risk ratio for tocilizumab in patients with moderate to severe RA in line with the original submission to NICE in February 2009

In Section 4.2 of the ACD the Committee has requested further information on the adverse event profile of tocilizumab. A full overview of the adverse event profile from the development programme was contained within the original submission. Here new data from the Japanese PMS and long term extension studies are presented. NICE had previously requested the study reports for the Japanese development studies which were supplied by Roche as part of the response to the ERG clarification questions.

The following data is the latest safety data from the Japanese Post Marketing Surveillance that has been through regulatory assessment. This was not available at the time of the original submission.

<u>Japanese post Marketing Surveillance Study</u>

In Japan Tocilizumab has been licensed for use in RA since April 2008. As part of the post marketing risk management plan as post marketing surveillance study has been commenced.

In the Japanese PMS study in RA, as of 25 Mar 2009, there have been 450 SAEs reported in 318 patients who received tocilizumab therapy out of the 5,426 RA patients enrolled (2,668 patient-years of exposure). This represents a SAE rate of 169 per 1000 patient-years (450/2668 patient-years). Most of the patients reporting SAEs were female (76.3%) with a median age of 62.5 years. The median age of the male patients is 60.4 years.

As of 25 Mar 2009, there were 27 fatal cases reported in the Japanese PMS (10.12 per 1000 patient-years). The estimated rate of death in the Japanese PMS program, as of 25 Mar 2009 was within the range of what has been reported in other RA PMS programs in Japan (see below).

Table 3: Summary of Data post from Post-marketing Surveillance Programs for Biologics in Rheumatoid Arthritis

	Post marketing Surveillance Programs		
	tocilizumab	Remicade	Enbrel
Number of patients	4915	7811	13894
Exposure (patient-years)	2135**	Ca. 3095***	Ca. 6947***
Deaths			
Number (%)	27 (0.50)	43 (0.55)	76 (0.55)
Rate (per 1000 patient years)	10.12	11	10.9
Serious adverse events (%)	5.8	6.2*	6.2

[1]Remicade, Mitsubishi-Tanabe Home Page, ARD 2008; [2]Enbrel, Wyeth Home Page

*Data from the first 5000 patients; **Exposure is lower as post marketing surveillance is ongoing; ***Estimated as if all patients exposed full 6 months.

Roche's review of the fatal cases revealed that in 14 of the 27 fatal cases, infection may have contributed to the fatal event. The mean age of the patients was 69.1 years and the majority were Steinbrocker Stage III/IV. In addition to the advanced age and RA disease, these patients had multiple medical conditions and were treated with various immunosuppressant agents in the past.

For a detailed list of all SAEs see Appendix III.

As with other biologic therapies for RA, the most frequently reported events were infections. In re-examining the cases with a fatal outcome, infection was noted as a contributing factor in 14 of the 27 deaths. It is important for clinicians to balance the efficacy of tocilizumab in the treatment of RA with the risk of a serious infection.

Further post marketing surveillance will also be commenced in the UK with tocilizumabs inclusion within the BSR Biologic Register. This inclusion is subject to contracts and the successful assessment by NICE.

Long-Term Safety and Tolerability of Tocilizumab Treatment in Patients with Rheumatoid Arthritis and a Mean Treatment Duration of 2.4 Years

The following data represents a pooled safety analysis of the phase III clinical trails and long term extension studies in patients who have received tocilizumab for a mean duration of 2.4 years. These data were presented at the ACR 2009 (Abstract 1955, Van Vollenhoven et al).

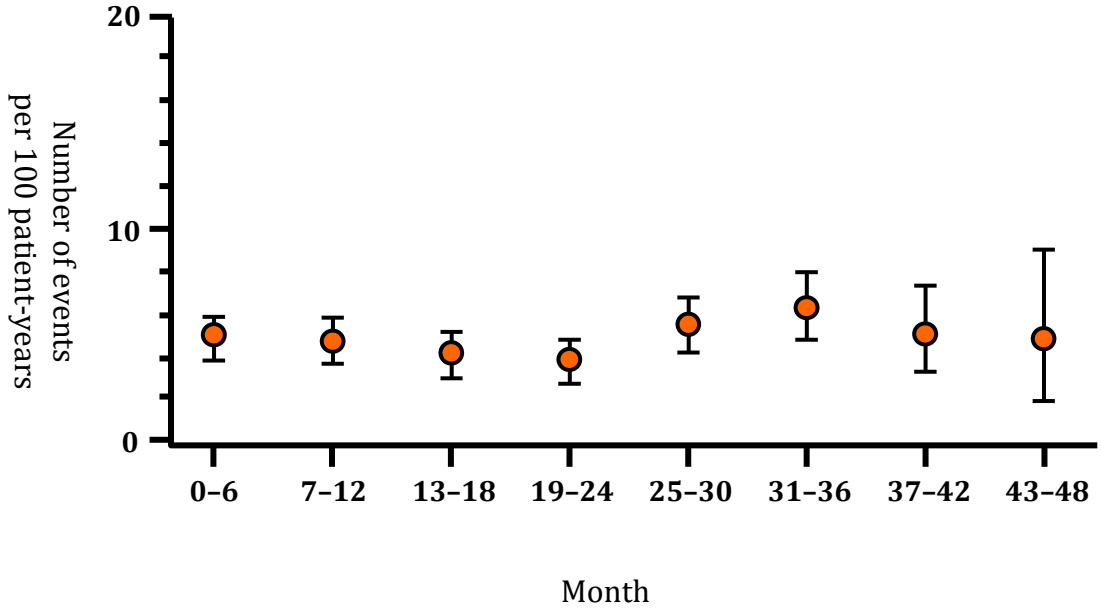
The population included all patients who received at least one dose of tocilizumab in the 24-week, phase III clinical trials (OPTION, AMBITION, RADIATE, TOWARD), in the phase III clinical trial (LITHE), in a phase 1 study, or in the ongoing, open-label extension studies. Safety data were pooled and analysed from the time of the initial tocilizumab exposure to the cut-off date of February 6, 2009.

Tocilizumab was administered to 4,009 patients, mean treatment duration was 2.4 years, and total treatment exposure was 9,414 patient-years. The rate of withdrawals because of adverse events was 5.8/100 patient years and was driven by elevated liver enzyme levels, infections, and benign and malignant neoplasms. The overall rate/100 patient-years of serious AEs was 14.91, of serious infections was 4.7, of deaths was 0.53, and of deaths from infection was 0.13.

Table 3: AEs, infections, and SAEs: Rates by 6-month periods (all-exposed population). Multiple occurrences of the exact same adverse event in one individual are counted as one event

	Rates/100 patient years (events) by 6-month periods							
	0–6	7–12	13–18	19–24	25–30	31–36	37–42	43–48
All AEs	470.9	356.2	296.9	292.0	274.7	272.5	253.4	273.3
Infections	128.3	112.1	100.9	103.2	97.1	101.6	99.2	102.3
SAEs	16.0	15.5	14.3	12.6	14.3	17.8	15.5	7.5

Figure 5: Serious Infections: Rates by 6-months periods (all-exposed population)



Rates/100 patient-years of upper and lower GI perforations were 0.01 for stomach/duodenum, 0.03 for small intestine, 0.02 for appendix, and 0.19 for large intestine. Malignancies occurred at an overall rate of 1.16/100 patient-years, without excess of any one type. Overall rates/100 patient-years for myocardial infarction and stroke were 0.25 and 0.19, respectively, and did not increase with tocilizumab exposure. Total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride levels increased at week 6 and remained relatively stable over time; 313 (7.8%) patients who initiated lipid-lowering therapy during treatment with tocilizumab generally responded to treatment without complications. The incidences of ALT and AST elevations >3× the upper limit of normal were 3.6% and 1.4%, respectively,

during the first 24 weeks of treatment, and the rates did not increase over time. Transaminase elevations were not associated with clinically apparent hepatitis or hepatic dysfunction.

Overall, these results demonstrate that no new safety signals have emerged with prolonged exposure to tocilizumab. Transaminase elevations were not associated with clinically important events. During longer-term treatment with tocilizumab (median duration greater than 2.5 years), the risks for AEs and serious AEs were stable over time and laboratory changes could be effectively managed. These data support a favourable benefit/risk ratio for tocilizumab in patients with moderate to severe RA and are in line with the safety dataset supplied in the original submission to NICE in February 2009.

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. To date NICE has failed to focus on the appropriate decision problem which has significant implications for future NHS clinical practice in the management of RA

NICE is using an inappropriate approach to the decision problem when considering likely future clinical practice. The remit of an STA can not preclude future use of existing NICE recommended therapies.

In the provisional guidance the Appraisal Committee has explored 5 different scenarios.

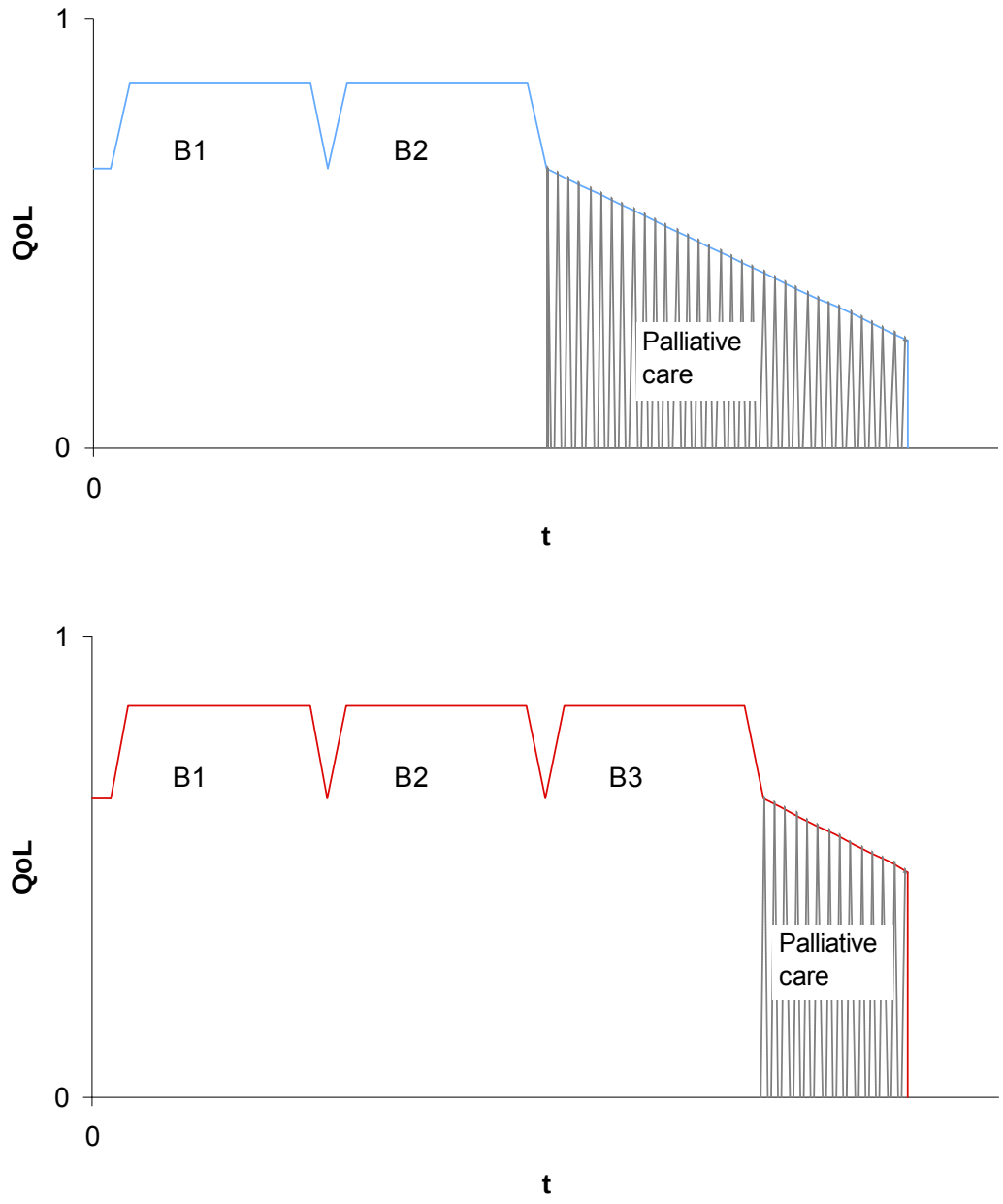
Scenario 1: Tocilizumab as a replacement therapy to the anti-TNFs
Scenario 2: Tocilizumab as an additive therapy in DMARD-IR
Scenario 3: Tocilizumab as a replacement therapy to rituximab
Scenario 4: Tocilizumab as an additive therapy in TNF-IR
Scenario 5: Tocilizumab as a therapy for rituximab inadequate responders

Roche is confident that consideration of scenarios 1 and 3 is not appropriate, as they do not evaluate how the management of RA can be improved through providing an additional treatment. These scenarios also regard RA as an acute episode rather than a chronic syndrome that needs a greater number of treatments to effectively manage a life-long disease.

Tocilizumab is the first in a new class of drugs offering inhibition of the IL-6 receptor therefore suppressing inflammation in a different way than TNF inhibition, B-cell depletion or selective T-cell co-stimulation modulation. Roche, echoing the clinical community's views understands that the future management of RA requires different types and classes of drugs in order to manage the chronic nature of RA in the most efficient and successful way. From a clinical point of view RA needs a wider choice of different class of drugs to combat debilitating disease progression. For many years RA has been considered a syndrome and therefore clinicians can assess whether one of the many tDMARDs will work in inhibiting early disease. If NICE's "one-in-one-out" approach was adopted only one tDMARD would be available to the NHS with unacceptable implications for many patients. Through application of these scenarios NICE would inhibit the introduction of new drug classes.

The Roche submission, consistent with previous RA appraisals, attempted to answer the question of whether it was cost effective to add an additional biologic to existing UK clinical practice and move the management strategy of RA from utilising 2 distinctly different classes of biologics to 3 distinctly different classes of biologics. The benefits of having 3 biologics rather than 2 are best illustrated in Figure 6 below.

Figure 6: Illustration of QoL over a lifetime for a patient receiving 2 biologics (B1 and B2; blue) and 3 biologics (B1, 2 and 3; red). The difference in the 2 graphs clearly indicate that the average patient accumulates more QoL if they receive 3 biologics instead of 2



** for illustration purposes only*

Moving from 2 biologics of different class to 3 biologics of different class has a profound effect on patients' QoL as illustrated in the figure above because patients spend less time in palliative care, a severely debilitating state which is also associated with high costs. Adding a treatment of different class of drugs to the existing RA management strategy can be a cost effective use of NHS resources as symptoms are controlled for a longer period of time.

Roche is certain that the most appropriate method of determining the cost effectiveness of tocilizumab is using the additive approach in both the DMARD-IR (scenario 2) and TNF-IR (scenario 4) settings.

With respect to the additional scenario (scenario 5) requested by NICE, Roche is unable to provide any cost effectiveness analysis due to the lack of available clinical data for tocilizumab in patients that have had an inadequate response to rituximab.

2. NICE fails to understand the dynamics and drivers of the tocilizumab economic model and ICER. Consequently a disproportionate focus has been placed upon parameters that do not significantly affect the cost effectiveness of tocilizumab

Several of the major points of uncertainty within the appraisal appear related to a lack of understanding in the relationship between certain clinical parameters and the estimation of the cost effectiveness of tocilizumab. Some of these key dynamics are summarised below which Roche believe are vital to reach a fair and accurate assessment of the most likely ICER for tocilizumab.

2.1. TNF inhibitors appear in both arms of the economic evaluation

As described in section 1 above, unless one assumes TNF inhibitors will be banned across the NHS as a result of the tocilizumab STA, one must include a TNF-inhibitor (or rituximab in the TNF IR setting) in both the intervention arm as well as the comparator arm in the economic evaluation. Therefore the assumed cost and efficacy of those treatments included within both arms of the model have a small impact on the final ICER.

Consequently the assumed ACR response rates for the anti-TNFs from the MTC, (as illustrated in original Roche submission) does not drive the final ICER. In addition, as illustrated in more detail in section 2.3, assuming a negative HAQ slope for all biologics has a limited impact on the ICER of tocilizumab.

2.2. Adding a biologic to existing standard of care reduces time spent in palliative care

As a result of the above characteristic, failure to account for the adverse events experienced within the palliative health care state will heavily bias the estimated ICER against an additional biologic. Time on an active treatment is similar across both arms of the model. Whilst the tocilizumab arm is exposed to an additional biologic it is exposed to a reduced period of palliative care, which includes drugs with significant adverse events (see section 3 paragraph 3.1 below). Therefore there could be a net reduction in adverse events from the use of an additional biologic.

The negative HAQ slope is applied to responding tocilizumab patients only and only for the period of time observed in the tocilizumab trials

Roche were mindful of not over-reaching the application of the observed negative HAQ slope within the tocilizumab phase III studies. Therefore it was only applied for the period it was observed within the trial. After this time-point a zero HAQ slope was applied for all patients remaining on treatment.

3. Several of the revised model parameters recommended in section 1.2 within the ACD are not reasonable or consistent with evidence based decision making.

Roche would firstly like to highlight that the key modelling uncertainties listed in section 1.2 affect both the DMARD-IR and TNF-IR indications. Any changes or consensus reached on the modelling parameters should also be applied in the DMARD IR indication/model as the ICERs share common inputs and subsequently follow similar values.

In this ACD response Roche addresses each modelling parameter separately and focuses on how the parameters are applied in RA modelling rather than how these parameters affect the cost effectiveness of the 2 indications. The cumulative impact of these changes are then illustrated in section 2, paragraph 3.

3.1. Exclusion of adverse event related disutilities and costs is unreasonable given the drug therapy in this late stages of the disease

Applying adverse events within the economic modelling of RA

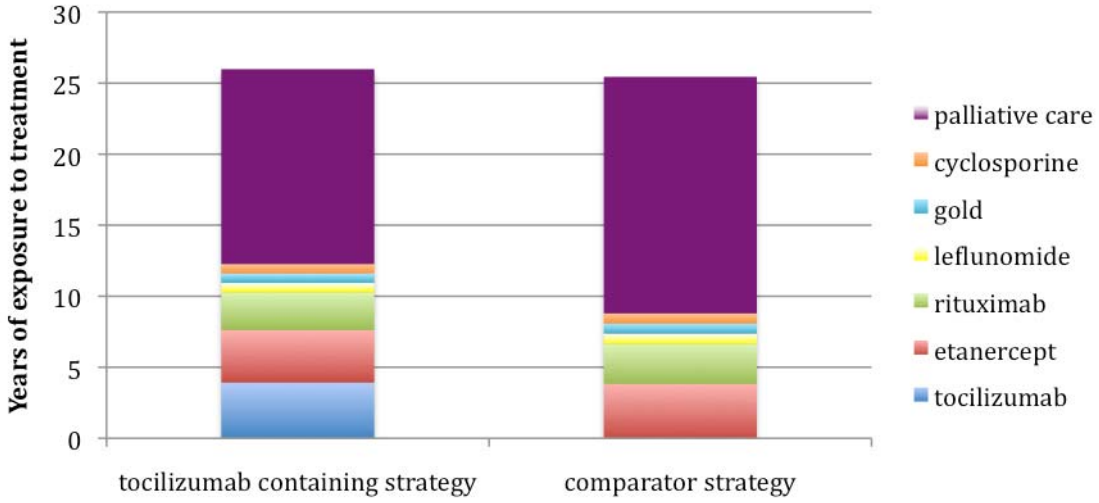
The most appropriate means of incorporating adverse events within an RA cost utility model is not a tocilizumab specific issue but relates to all past and future RA appraisals.

Inclusion of AEs in economic modelling performed by NICE or manufacturers has been very rare in RA to date, setting a strong precedent of positive guidance without any analysis of AEs within the respective cost effectiveness analysis. It is unclear why this has now been requested to be included in the Roche analysis. It is also not possible to incorporate adverse events in a method consistent with the NICE Guide to Methods in the time available following the request.

Deriving robust AEs cost and dis-utilities would require a series of patient-reported outcomes studies using the EQ-5D to determine the utility decrement associated with each adverse event experienced. In addition a time and motion study to estimate the medical resource utilisation associated with all adverse events would be necessary. These studies take several months (or even years) for the design, implementation, data collection and analysis phases. It is therefore unfeasible for Roche to perform these in 4 weeks and only rudimentary estimates are possible.

Responding to the 1st ACD, Roche previously attempted to address the issue of AEs within the economic model. Although the 0.05 utility decrement used by the ERG was arbitrary, Roche utilised it to assess the impact of AEs in the economic model and showed that it has no effect on the cost effectiveness of tocilizumab. Roche accepts that in the additive scenarios patients are exposed to additional biologic treatment related AEs. However the total patient exposure to treatment remains equal across both arms. This is best illustrated in the figure below.

Figure 7: Years of treatment exposure by treatment arm in DMARD-IR analysis



The figure above demonstrates that patients remain on treatment for an equal amount of time. Exposure to treatment and treatment related AEs remain constant across the two arms. However the proportion of time patients are exposed to biologic side effects compared to palliative care side effect is different.

To assume that there is no utility decrement associated with AEs seen in palliative care, as was suggested in the ERG tocilizumab ICER, is both un- realistic and biased against the additive biologic.

For more details on drugs and adverse events experienced in palliative care see Appendix IV.

Therefore Roche believe that utilising a utility decrement and/or cost in the modelling of RA should be applied in all cycles for which patients are on treatment <u>including</u> palliative care.

3.2. <u>The HAQ-Utility mapping mechanism used in the Roche submission has been replicated in light of new evidence and reanalysis undertaken by Birmingham university</u>

Roche, as part of the response to the 1st ACD, provided additional data supporting the non-linear relationship between HAQ and Utility as used in the cost effectiveness analysis. The Appraisal Committee has not conisderd this credible evidence, based upon tocilizumab phase III data using the EQ-5D and has requested that Roche uses an equation from Bansback et al (2005) based upon the HUI3 non-reference case instrument.

It is unclear why the committee prefers the Bansback mapping method over the Roche method when considering their relative characteristics and merits in light of the guide to methods. In addition Roche would like to highlight that a sensitivity analysis using the linear mechanism has already been provided as part of the original Roche submission.

Since the publication of the 2nd ACD Roche has had access to the MTA Assessment Group report of “Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor”. The report was

produced by the West Midlands Health Technology Assessment Collaboration (Birmingham) which is the same independent academic group as the appointed ERG in the appraisal of tocilizumab. Given that the appraisal is an MTA, the academic group received evidence from all manufacturers involved (Abbott, Wyeth, BMS, Schering Plough and Roche) but also conducted its own independent analysis and modelling exercise.

Under the heading "Quality of life (QoL) scores" of the report, the AG provides its preferred HAQ-Utility mapping mechanism. The mechanism derived by the AG echoes Roche's submission and defines the relationship of HAQ and utility as a quadratic function.

HAQ-U mapping equation – Roche submission:

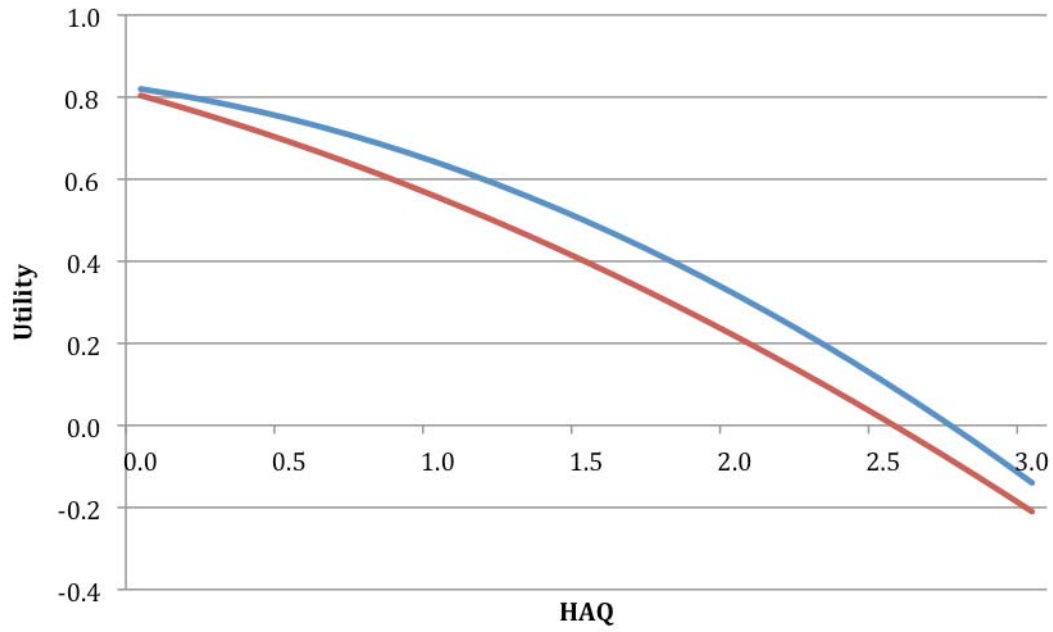
$QoL=0.82-0.11*HAQ-0.07*\ HAQ^2$

HAQ-U mapping equation – Assessment Group independent review:

$QoL=0.80\tilde{4}0.203*HA\tilde{Q}-0.045*HAQ^2$

The 2 equations are graphically presented in the figure below.

Figure 8: Graphic representation of the Roche (blue) and Assessment Group derived mapping equations (red)



The Birmingham mapping mechanism was derived by reanalysing the Hurst data (MTA Assessment Group report). The description on the report does not provide the methodology with which the mechanism was derived but it can be assumed that a function that includes a quadratic term provided the best fit to the available data. The Birmingham group criticised the approach taken by Roche in the tocilizumab STA, which is has now actually been adopted and endorsed by the AG within the RA MTA.

Roche applied the Birmingham mapping mechanism to the economic model in order to explore the impact of this alternative assumption into the cost effectiveness of tocilizumab and found that the impact is minimal. The results can be found in the table below.

Table 4: Cost effectiveness of tocilizumab in DMARD-IR and TNF-IR utilising alternative mapping mechanisms

	Tocilizumab submission mapping	Birmingham Assessment Group report mapping
DMARD-IR	**£19,870 per QALY**	**£19,685 per QALY**
TNF-IR	**£22,003 per QALY**	**£22,523 per QALY**

The emergence of this new mapping mechanism coupled with previously submitted evidence indicating the non-linear relationship between HAQ and utility is the optimum (Boggs et al 2002) suggests the application of a linear method based on HUI3, instead of utilising the tocilizumab phase III EQ-5D data (Ducournau et al 2009) is highly inappropriate.

3.3. Disregarding tocilizumab's long-term HAQ data is unreasonable and unfair since the NICE Guide to Methods indicates that utilisation of phase III data represents the most appropriate evidence base

The committee has consistently and unfairly disregarded the long-term HAQ data from the tocilizumab trials. It appears that NICE is instructing Roche to assume a zero HAQ slope for tocilizumab solely due to the absence of any similar evidence being available for other treatments in the treatment strategy. Roche is certain that ignoring this data is unfair and unreasonable and that it goes against the NICE Guide to Methods and evidence based decision-making.

The committee also seems to misunderstand that the additive approach employed by Roche is not attempting to prove that tocilizumab is superior to other biological therapies but simply to utilise the best available evidence. The decision problem as defined by Roche utilises etanercept and rituximab in both the tocilizumab containing and comparator sequences (in DMARD-IR). In this way the HAQ slope of the other treatments plays a limited role in the cost effectiveness analysis role as they appear in both arms.

Based on the additive approach to cost effectiveness and the fact that other biologic treatments appear in both arms of the economic model Roche believe that it is erroneous to disregard the long follow-up from the tocilizumab trials as it is not comparative data versus anti-TNFs (as outlined in section 1.1).

To illustrate this point Roche has performed a sensitivity analysis where a negative slope equal to that found in the tocilizumab trials is assumed for all biologic treatments in the cost effectiveness analysis. This is a major assumption as no such improvement in HAQ score has ever been observed in any of the trials or published studies for the other biologic therapies. The cost effectiveness results from modelling the negative slope observed in the tocilizumab trials for all bDMARDs can be found in the table below.

Table 5: ICERs based on an sensitivity analysis that assumes a negative slope for all bDMARDs

	Tocilizumab submission	Sensitivity analysis assuming negative slope for all bDMARDs
DMARD-IR	**£19,870 per QALY**	**£25,459 per QALY**

TNF-IR	**£22,003 per QALY**	**£24,237 per QALY**

3.4. The committee amendment to patient weight disregards the available evidence

Since the tocilizumab dose is based on patient weight, the economic evaluation should regard this important parameter in relation to the clinical evidence. An assumption on the average weight of patients (75 kg) without due consideration of the distribution of weight in the treated population does not reflect the weight distribution observed in the tocilizumab clinical trials and offers a simplistic suggestion of this model parameter.

The economic evaluation follows the NICE reference case and reflects the reported clinical outcomes (ACR response, HAQ score etc.) in line with the appropriate patient characteristics. To assign different patient characteristics from that of the clinical trial departs from the standard methods of economic evaluation, as required by NICE, and renders the cost-effectiveness estimates invalid.

It is noted that the assumption of 75kg, believed to reflect the average BSRBR patient, was accepted as credible by the committee following consultation comments submitted by the manufacturer of a competitor product based upon data on patient weight in the BSR registry. However, based on commercial rights, different parties of BSR (manufacturers) have access to different patient data. In contrast to the current data accepted by the committee, in the drafting process of the NICE technology appraisal 130 (October 2007), one of the manufacturers provided data from the BSRBR suggesting that 42% of patients in that sample weighed below 67 kg (Schering-Plough comments on assessment report and appeal on FAD document). Therefore, the basis of the 75kg assumption is questionable and contradicts the historical precedence set in past RA appraisals and recent MTA which have consistently considered the average patient weight to be 70kg (page 213 MTA Assessment Group Report).

To estimate the annual acquisition cost of tocilizumab individual patient data from the clinical trials was analysed. This has not been considered by the committee.

According to the licence, tocilizumab is given to all patients at a dose of 8mg per kg. A minimum dose is also applied to patients with weight less than 60kg. Tocilizumab comes in three different vial sizes (80mg, 100mg and 200mg) and combinations of them help to minimise wastage.

Since the UK patient sample in the tocilizumab phase III trial programme was limited (~30 patients), the EU weight distribution was used as a proxy. The individual patient data on weight was taken from the DMARD-IR trials and TNF-IR trial separately. The individual dose for each patient was estimated and given the available vial combinations, a cost per patient and the average cost for the EU sample was calculated. Moreover, the observed dose data suggest that in both the DMARD-IR and TNF-IR indications patients received only 93% of the planned doses. If this is applied to the 13 infusions that a patient receives per annum, the average number of

infusions per annum is decreased to 12.1. With the adjustment of the missed doses the average acquisition cost for tocilizumab is estimated to be around £9,100 accounting for wastage, missed doses and EU patient weight in the trials.

Furthermore, the SPC permits dose reductions to 4mg/kg which was not permitted in the clinical studies and tocilizumab's forthcoming licence update (filed with the regulators; expected approval May 2010) restricts the maximum dose to 800mg creating a ceiling effect for all patients weighing over 100kg. It follows that in the real world setting these factors may reduce the average tocilizumab dose below 8mg/kg.

Therefore, having considered all available evidence the average cost of £9,295 per annum per patient – reflecting a 70kg patient receiving all doses- appears both a reasonable and conservative estimate in light of the evidence.

3.5. The committee's amendment to the administration cost is an inflated representation of the true opportunity cost to the NHS of tocilizumab drug administration.

Roche believe that the inflated HRG administration cost suggested by consultees and the committee overestimates the true opportunity cost incurred by NHS. The issue of the cost of administration has been examined by the ERG and discussed in the 1st Appraisal Committee meeting.

The committee, wanting to understand the complexity of administering tocilizumab in routine clinical practice, requested further clarification from the clinical experts present at the meeting. Both clinical experts that responded to this question have had experience with the administration of tocilizumab. The response was categorical that the administration is simple and patients come, in practice, for an hour and leave without any complications. This suggests patients do not normally spend more than 1 hour in hospital and that assuming costs for administering the drug for half a day, as requested within the ACD is excessive.

As part of the evidence generation for tocilizumab Roche conducted a time-and-motion study (pH Associates 2008; Roche data on file) in 3 centres to determine the medical resource utilisation associated with tocilizumab infusion. The baseline characteristics of the patients can be found in Appendix V. Results from 13 tocilizumab patients shows that mean infusion time was 1 hour 4 minutes (sd: 5 min 40 sec) which reinforces that tocilizumab administration is uncomplicated and takes consistently 1 hour to infuse echoing the clinical experts' opinion.

Roche believe that estimating the cost of infusion based on the above evidence, expert opinion and historical precedence set by previous RA technology appraisals suggest the best approximation of the true opportunity cost to the NHS is £154 per infusion.

The recently distributed independent review published by the Birmingham Assessment Group supports this assumption. The cost per administration has been evaluated at £142 per infusion. This figure is inflated from the figure of £124 used in earlier versions of the Birmingham model (BRAM).

In light of all the above evidence Roche firmly believe that £154 reflects the true cost of administering tocilizumab. However Roche accepts that the uncertainty around this point estimate exists due to difference in practices between trusts. According to the NICE guide to methods this uncertainty is best explored by including the variable in the probabilistic sensitivity analysis (PSA). Roche did include the cost of

administration in the PSA performed (mean = 154.3, CIs: 92.58, 216.02) as part of the original submission and subsequent response to the 1st ACD therefore addressing the committee's concerns over an increased cost of administration.

4. Utilising the most appropriate decision problem and selecting model parameters based upon the spirit of evidence based decision making and the NICE Guide to Methods demonstrates the most plausible ICER for Tocilizumab is less than £30k per QALY in <u>both</u> indications

The table below summarises the updated ICERs for tocilizumab in both the DMARD IR and TNF IR settings. The ICERs are based upon a thorough consideration of the latest ACD requests and criticisms and subsequent selection of model parameters. As discussed above for each parameter the selection has been based upon the best available evidence and methods considered most consistent with the spirit of the NICE guide to methods. The reported ICERs represent the cumulative impact of the changes.

Table 6: Summary of economic model refinements and revised Roche cost effectiveness estimates

Model Assumption	Roche revised model – 2nd ACD – ICER – DMARD-IR	Roche revised model – 2nd ACD – ICER – TNF-IR
Roche base case	£19,870 per QALY	£22,003 per QALY
Using un-pooled MTC estimates	£20,250 per QALY	N/A
Withdrawal rate of etanercept used	£20,166 per QALY	N/A
Negative (3 years in DMARD-IR; 2.5 years in TNF-IR) and rebound effect (Back to baseline)	£22,003 per QALY	£22,876 per QALY
AE utility decrement equal to 0.05 per cycle	No Change	No Change
Administration cost equal to £154.3	£20,334 per QALY	22,428 per QALY
Exponential long-tem HAQ modelling	£18,704	£19,478
Cumulative Impact of Changes	**£23,655 per QALY**	**23,318 per QALY**

5. The ACD fails to give adequate consideration to updated cost effectiveness analysis submitted by Roche as part of the first ACD consultation in its consideration of the evidence.

As part of the 1st ACD consultation, Roche submitted an updated cost effectiveness of tocilizumab after a careful and thorough consideration of the criticisms contained within both the ERG report and ACD. Roche accepted some criticisms and attempted to provide further clarification and justification around other model parameters.

A careful and evidence based approach in the selection of several key model parameters is imperative to reach a credible estimate of the ICER for tocilizumab. Given the ICER for tocilizumab is in the region of the NICE threshold, the importance of this exercise can not be understated.

In light of the 2nd ACD and the discussion that took place in the 2nd Appraisal Committee meeting Roche believes that the updated information, data and analysis have inadequately been taken into consideration in determining the most plausible estimate of the cost effectiveness of tocilizumab. It is unclear whether the committee reached a consensus on the validity of the Roche reanalysis or whether the ERG had the opportunity to assess the robustness of the additional information provided by Roche.

In more detail the specific parameters covered extensively in the Roche response include:

5.1. Rebound effect

Amendments to the economic model made in light of the ERG criticisms of the size of the rebound effect. The updated version of this modelling parameter allowed patients to return to baseline HAQ following treatment failure. The analysis illustrated that the ICER rises by only ~£2,000 (in DMARD-IR) as a result of this refinement. Reanalysis of the TNF-IR showed a minor rise in the ICER.

5.2. Adverse Event impact on Quality of Life

Roche disagreed on the approach taken by the ERG in applying a 0.05 utility decrement to all treatment cycles except for palliative care. The approach was not justified and went against opinion voiced by the clinical community suggesting that the adverse event profile and the impact on patient's QoL is at least similar to a biologic treatment when this is added in the treatment algorithm. Roche estimated the cost effectiveness analysis applying the 0.05 utility decrement due to adverse events to all treatment cycles including those patients spend on palliative care. The adoption of this assumption had a negative impact on the overall benefit gained by patients in both the tocilizumab and comparator strategy but not net difference in the ICERs in either of the indications.

5.3. Mapping

Roche argued that using EQ-5D utilities directly from the tocilizumab trials within the model, was not possible as no comparable data is available for other RA therapies included within the model. This is the reason why Roche resorted to using a mapping mechanism. This is why a mapping mechanism has been used virtually all other manufacturers'' submissions to NICE for RA relative biologics. Roche provided further evidence supporting the non-linear mapping mechanism including a break down of frequencies of HAQ and EQ-5D (both collected in the trials) data. Neither

were these data discussed nor were they taken into consideration when deciding that tocilizumab is not a cost effective solution in DMARD-IR.

Recent evidence found above support Roche's assertion that the HAQ-Utility relationship is best described by a non-linear function.

5.4. Long-term HAQ data

Roche demonstrated that data from tocilizumab's phase III trials show a long-term negative HAQ slope. Roche provided a later cut-off of the HAQ data showing a sustained HAQ improvement in responding patients. Further to ERG's comments on fitting a favourable function in the long-term data, Roche explored the fit of alternative models. These actually improved the ICER but the 2nd ACD failed to acknowledge this.

Roche is committed to use the most up-to-date evidence base over assumptions and opinions and has obtained a further cut-off of the HAQ data from tocilizumab phase III program that confirms and strengthens the trends observed in the original submission and the subsequent response to 1st ACD.

5.5. The committee suggestions and conclusions on the MTC are in error

ACD section 4.5: "*The Committee noted that there was not formal mixed treatment comparison that excluded both the large trial with high control arm response rates and the trial that had low control arm response rates*"

The ACD fails to acknowledge the updated MTC results provide by Roche as part of the response to the 1st ACD. Roche reanalysed the MTC excluding the Moreland study (low control arm response rates) and the Klareskog study (high response rates) and provided an updated estimation of the response rates. In addition Roche performed a sensitivity analysis on the economic model based on these revised point estimates and demonstrated that the model is insensitive to fluctuation of the response estimates of other biologics in the treatment sequence in the additive approach to the decision problem.

ACD section 4.6: "*…, in the DMARD-IR population, etanercept would be expected to dominate tocilizumab.*"

Roche developed the MTC to identify response rates for each biologic for inclusion in the model. The MTC is not adequate to definitively identify superior and inferior clinical effectiveness, but it is the optimal method for obtaining credible, replicable, and evidenced based response rate point estimates for economic modelling. It is unclear to Roche why the Committee suggests that etanercept is more effective compared to tocilizumab (dominance implies that etanercept is more effective and less costly) and bases the conclusion of the comparative efficacy on ACR response rates while ignoring other relevant clinical endpoints such as the long-term HAQ change while on treatment.

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 2nd ACD is not a suitable basis for the preparation of guidance for the reasons outlined in sections 1 and 2 above. In particular, NICE utilizes the replacement approach to the decision problem in evaluating the cost effectiveness of tocilizumab in both DMARD-IR and TNF-IR. In addition NICE requested Roche to provide a cost effectiveness analysis in a patient population in which tocilizumab was examined in terms of its efficacy and safety (scenario 5). Finally the ACD failed to fully consider and reflect the comments on modelling parameters Roche submitted as part of the 1st round of consultation.

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

Roche believe that NICE's assessment of tocilizumab's cost effectiveness is inequitable and unfair in the context of the decision making criteria applied in the evaluation of previous biologic therapies for RA.

ICER values considered acceptable by the committee

Following the re-estimation of the DMARD-IR and TNF-IR ICERs Roche believe that NICE will be acting unfairly and inequitably if it rejects tocilizumab on the basis of cost effectiveness as the ICERs in both indications are in the range of previously recommended ICER in RA. In TA 130 NICE assessed the anti-TNFs using the same additive approach employed by Roche and recommended the use of the anti-TNFs in DMARD-IR with ICERs of £28,000, £37,600 and £46,100 for etanercept, adalimumab and infliximab respectively.

In TA130 NICE approached the decision problem using an additive method and not a replacement approach as used in the provisional guidance for scenarios 2 and 4. Using a replacement approach in TA130 appraisal would have resulted in only anti-TNF clearly dominating the other 2. Instead NICE used an additive approached in which the anti-TNFs where added to the existing treatment strategy in order to answer the question whether adding a biologic treatment is cost effective and an effective use of NHS resources. NICE never considered choosing one of the anti-TNFs even though the Assessment Group as part of the appraisal process presented this comparison.

Roche firmly believe that the approach historically taken by NICE is a fair and methodologically correct approach and answers the question of whether adding treatments to the best current treatment strategy of a chronic condition is cost effective. NICE needs to adopt the same approach in this appraisal in order to be equitable and to retain consistency and credibility amongst all RA appraisals.

Inconsistent approach to evaluating and recommending multiple treatment options within RA

In the previous evaluation of anti-TNFs in TA130, no attempt was made to make head to head evaluations of the relative costs and effects across the 3

available anti-TNF therapies. Instead NICE considered if using a TNF in addition to existing standard of care was cost effective. With relatively high ICERs, NICE were subsequently happy to make all 3 available and allow clinicians to select the one considered most appropriate for the respective patient.

However for tocilizumab, a head-to-head comparison has been considered appropriate and played a significant role in the current negative decision. Had a similar approach been adopted for the anti-TNF evaluation, differences in the cost and effectiveness of the TNFs would have also been observed. This would also lead to issues of alleged dominance between TNFs. However NICE considered it appropriate to allow all 3 TNFs to be made available and permit the clinician to select the treatment of choice.

Appendix I

Patient numbers, mean HAQ scores and CIs supporting the long-term HAQ data.

DMARD-IR November 2009

wk	Patient No.	Mean	95% CI	
1	1340	1.5124	1.479472	1.545328
12	1333	1.1069	1.070248	1.143552
24	1258	1.0205	0.982672	1.058524
36	1131	0.9813	0.94112	1.02148
48	1102	0.9441	0.903724	0.984476
60	1075	0.9417	0.90152	0.98188
72	1048	0.9236	0.88244	0.964956
84	755	0.8943	0.845496	0.9433
96	1029	0.8945	0.853928	0.935268
108	990	0.8878	0.844876	0.930724
120	967	0.8601	0.817372	0.902632
132	954	0.8475	0.804772	0.890424
144	923	0.8604	0.816692	0.903912
156	888	0.8411	0.796412	0.885592
168	714	0.8232	0.772828	0.873572
180	569	0.8383	0.78146	0.895336
192	381	0.8131	0.745872	0.880328
204	253	0.8128	0.729696	0.8961
216	100	0.8825	0.739812	1.025188
228	24	0.7448	0.442764	1.046836

TNF-IR November 2009

wk	Patient No.	Mean	95% CI	
1	175	1.7384	1.650592	1.826208
12	175	1.4364	1.332128	1.540868
24	155	1.3516	1.24184	1.46136
36	137	1.2737	1.154924	1.392476
48	132	1.3098	1.194748	1.424852
60	123	1.2683	1.14384	1.39276
72	118	1.16	1.027112	1.292692
84	113	1.1974	1.06216	1.33264
96	106	1.207	1.068232	1.345964
108	107	1.1928	1.0556	1.33
120	100	1.2125	1.074516	1.350484
132	96	1.1453	0.997124	1.293476
144	98	1.0995	0.9574	1.241404
156	91	1.1319	0.974708	1.289092
168	66	1.0814	0.895004	1.267992
180	43	1.1017	0.880416	1.32318
192	24	1.125	0.818848	1.431152
204	11	1.1023	0.620336	1.584264

Appendix II

Patient numbers, mean EQ-5D and CIs from the phase III LITHE trial

Placebo + MTX November 2009

Day	Patient No.	Mean	95% CI	
1	380	0.3982	0.36488	0.43152
56	350	0.4849	0.453932	0.516064
112	337	0.5051	0.471976	0.53842
168	205	0.6015	0.567396	0.635604
224	178	0.6207	0.58444	0.657156
280	164	0.6066	0.567988	0.645212
364	142	0.5941	0.551372	0.637024
448	25	0.6879	0.61146	0.76434
532	27	0.6432	0.579892	0.706312
644	21	0.6688	0.55414	0.78346
728	19	0.5907	0.472316	0.70928

8mg tocilizumab + MTX November 2009

Day	Patient No.	Mean	95% CI	
1	389	0.4143	0.38294	0.44566
56	367	0.5781	0.551248	0.604952
112	336	0.6034	0.57694	0.62986
168	303	0.6395	0.61402	0.66498
224	281	0.6404	0.612568	0.668232
280	277	0.6471	0.61966	0.67454
364	241	0.6543	0.6249	0.683896
448	79	0.7215	0.672696	0.7705
532	65	0.6989	0.639512	0.758092
644	53	0.748	0.688416	0.807388
728	46	0.7447	0.68688	0.802324

Appendix III

Serious Infections

One hundred and forty-three patients reported a total of 174 infections, of which 140 were serious, yielding a rate of 52 per 1000 patient-years. The most frequently reported event was pneumonia and related terms (n=35), yielding a rate of 13 per 1000 patient years.

The background rate for pneumonia requiring hospitalization in a non-Japanese RA population was reported at a rate of 8.4 per 1000 patient-years**.** When comparing the rate for pneumonia in the Japanese PMS to the background rate in younger, non-Japanese RA patients, the rate in the Japanese PMS is higher. In PMS studies conducted in Japan with a similar population receiving biologics (infliximab and etanercept), the incidence of bacterial pneumonia is higher than that reported in the ongoing Japanese tocilizumab PMS study (0.7%; 35/5426). Oka et al (2006) reported on the experience of 5000 patients with active RA who were treated with infliximab, and noted that 2.2% of the patients experienced bacterial pneumonia Miyasaki et al (2006) reported on the experience of 4000 patients with RA treated with etanercept, and noted that 2% of their treated patients experienced bacterial pneumonia as an SAE.

Opportunistic Infections

The overall rate for opportunistic infections in the Japanese PMS program for tocilizumab was 10.5 per 1000 patient-years. In a recent article on opportunistic infections in patients treated with infliximab, it was reported that 9.5% of patients experienced an opportunistic infection. Using the mean person years of follow-up, the rate per 1000 patient years is 25.1.

• There were four reports of TB and related terms. The rate of TB for the Japanese PMS program is 1.4 per 1000 patient years which is within the range of the rate of TB reported with TNF-blockers, 2.57 per 1000 patient-years in non-Japanese patients

• There were five reports of Pneumocystis jiroveci pneumonia (PJP). A review of the five PJP cases revealed that the patients' ages ranged from 61 to 73 years (median age of 72 years). In two of the five cases, the patients had a previous history of an opportunistic infection. In one fatal case (MCN 608652), the patient had a history of Cytomegalovirus gastroenteritis and rituximab was given five months before the diagnosis of PJP. The incidences of PJP in the PMS studies for infliximab and etanercept in Japan were 0.4% and 0.23%, respectively; in comparison the authors cite as the corresponding incidence reported in the US a rate of ~0.01%. The rate of PJP cases for the Japanese PMS for tocilizumab is 1.9 per 1000 patient-years.

• There were 11 reports of herpes zoster and one case of herpes encephalitis considered serious. The rate for herpes zoster for the Japanese PMS for tocilizumab is 4.1 per 1000 patient-years, which is within the expected range for the background rate from the literature of 9.83 to 13.3 per 1000 patient-years.

Cardiovascular Events

The comparison of the Japanese tocilizumab PMS event rates appear to be aligned with the rates in the published literature for strokes and MI.

• There were 12 cases of stroke (two cerebellar infarction, one cerebral haemorrhage, five cerebral infarction, one intraventricular haemorrhage, and three subarachnoid haemorrhage). The Japanese tocilizumab PMS rate for stroke is 4.5 per 1000 patient years, which is in range with the background rate in the RA population from the literature of 5.1 per 1000 patient-years.

• There were six cases of MI. The Japanese tocilizumab PMS rate for MI is 2.25 per 1000 patient-years, which is in range with the background rate in the RA population from the literature of 5.3 per 1000 patient-years.

Summary

Overall, the comparison of the Japanese tocilizumab PMS event rates appear to be aligned with the rates in the published literature for MIs, stroke, TB, and herpes zoster. The PMS rates for pneumonia and opportunistic infections, however, could not be clearly ascertained as in range with the published background rates in RA. One limitation for the comparison lies with the greater proportion of the elderly patients in the PMS in comparison with the RA, non-Japanese populations cited in the literature.

Appendix IV

Palliative Care Adverse Events

As reported in the response to the 1st ACD, Roche consulted with clinical experts and found that the palliative care portion of a patient's treatment contains a set of drug therapies including glucocorticoids in high doses and pain control medications along with cytotoxics and immunosuppressants.

Palliative care is applicable for those patients who have unfortunately either failed to respond, lost response or cannot tolerate existing non-biologic and biologic DMARDs. Management of these patients then looks to alternative treatments that range from consideration of stem cell transplant and the initiation of potent cytotoxics such as cyclophosphamide to surgery. Supportive care through use of high dose steroids and analgesics is very commonly utilised. Hospital in-patient stays for management of acute episodes tend to be more frequent as is outpatient and community based follow up. The impact on the patient in terms of disability and reduced functional capacity may also result in increasing burden on social services and family carers not to mention the impact on employment of both the patient and those who take on the responsibility of caring for them.

Rheumatoid arthritis currently has no cure however the advent of biologic therapies has considerably delayed the onset of palliative care for a large number of patients. Despite the delay, nearly all patients will lose their response to anti rheumatoid therapy and some time spent in palliative care cannot be avoided. To be able to limit the amount of time a patient spends in palliative care additional treatment options are required.

For those patients receiving palliative care and their clinical team a balance between symptomatic relief and the adverse events that occur with the increased use of various palliative therapies such as steroids and analgesics (both NSAIDs and opioid based), gold, cyclophosphamide and cyclosporin must be found. Steroids such as prednisolone are widely used in palliative care and these are often used in high doses for protracted periods of time and in many cases cannot be withdrawn. The adverse event rates associated with steroid use are well documented and can be related to both dose (Saag et al, 1994) and duration of exposure. Renal, musculoskeletal, metabolic, endocrine, dermatological, gastrointestinal, neurological and ophthalmic adverse events are all seen and it is recognised that the addition of steroids to existing biologic and traditional DMARDs increases the likelihood of infection (Trejos et al, 2009). It would be reasonable to assume the same association would be seen with the use of steroids with cyclophosphamide and cyclosporine for example.

Curtis et al, 2006 used population based assessments of corticosteroid induced AE to demonstrate that for those patients taking steroids for greater than 60 days with a mean dose of 16mg/day 90% reported at least one AE with 55% of patients reporting an AE as bothersome. 12% reported a fracture for example, with 15% reporting cataracts. This doesn't account for the unseen non-reportable AE such as osteoporosis, hypertension and glucose intolerance.

Palliative care will also result in increased dependence on both NSAID and opioid-based analgesics for pain control. As with corticosteroids these will be used in higher doses and for greater intervals than for those patients effectively managed by traditional and biologic DMARDs. Again the AE profile of NSAIDs (COX1) is well documented with gastrointestinal symptoms reported by significant number of

patients (>10%) (Singh G et al, 1997) The combination use of steroids and NSAIDs exacerbates the frequency of GI adverse events.

Palliative care, as stated previously may also involve the use of cyclophosphamide, cyclosporine and gold for example all of which has well characterised AE profiles, some of which are life threatening (eg myelosuppresion, sepsis and malignancy with cyclophosphamide). Rates of surgery increase with increasing disability in rheumatoid arthritis patients and thus the postoperative complications should also be considered as AE's of palliative care.

It is apparent as the evidence above suggests that the drugs and non-pharmacological interventions used in palliative care can have a profound effect on patients' quality of life. The AEs seen with palliative care can be considered to be as significant, if not more significant than non-palliative treatment strategies. In addition, the management of palliative care and its associated AEs would incur a substantial cost to the NHS with increased in-patient and out-patient episodes and to society as a whole with the requirement for earlier community based support in the form of family carers and social services input. The addition of tocilizumab in the treatment strategy delays the progression of patients to palliative care and therefore an average patient spends less time in this stage of the disease.

Appendix V

Time-and-motion patient baseline characteristics:

Demographic	All centres (3) (n=13)
Mean age	60.3
Median age	62.0
Age range	38.0-76.0
% male	50

References:

van Vollenhoven, Ronald F., Siri, D., Furie, R., Krasnow, J., Alecock, E., Alten, R.; Long-Term Safety and Tolerability of Tocilizumab Treatment in Patients with Rheumatoid Arthritis and a Mean Treatment Duration of 2.4 Years [abstract]. *Arthritis Rheum* 2009;60 Suppl 10 :1955

Oka H, Nishioka K, Togo M, and Ochi T. The efficacy of infliximab for patients with rheumatoid arthritis in Japan: results of 5000 cases of post-marketing surveillance data. APLAR *J Rheumatol.* 2006; 9:142-145.

Miyasaka N, Takeuchi T, Eguchi K. Guidelines for the proper use of etanercept in Japan. *Mod Rheumatol*. 2006; 16:63-67

Trejos, Eduardo Bonilla, Hannon, Michael J., Skanderson, Melissa, Good, Chester, Kwoh, C. Kent; Risk of Infection in Rheumatoid Arthritis Associated with Use of Anti-TNF Agents, DMARDS and/or Prednisone [abstract]. *Arthritis Rheum* 2009;60 Suppl 10 :2058

Singh G, Ramey DR. NSAID induced gastrointestinal complications: the ARAMIS perspective—1997. *J Rheumatol* 1998; 25 (suppl 51):8–16

Curtis et al, Population-based assessment of adverse events associated with long-term glucocorticoid use *Arthritis & Rheumatism (Arthritis Care & Research)* Vol. 55, No. 3, June 15, 2006, pp 420–426

Saag et al, Low dose long-term corticosteroid therapy in rheumatoid arthritis: An analysis of serious adverse events *American Journal of Medicine*, 1994, Volume 96, Issue 2, Pages 115-123

[redacted]

Thursday 18th February 2010

Kate Moore
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

BY E-MAIL

Dear Kate,

SINGLE TECHNOLOGY APPRAISAL – Tocilizumab for the treatment of rheumatoid arthritis ICER Clarification

Thank you for giving us the opportunity to clarify the possible errors identified by the committee in relation to the ICERs reported within the previous Roche ACD responses.

As correctly identified by the committee there was an error in table 3 of the Roche response to the first ACD, this created the situation that when observing the reported incremental costs and QALYs the ICER for the un-pooled MTC scenario were in the region of £70,000. As previous sensitivity analysis relating to ACR responses rates has illustrated, this is implausible given the actual changes to the ACRs that occur from the pooling or unpooling methods. This is explained by a typographical error.

In the process of validating and replicating these results, Roche has also identified a small error when utilising the ERG recommended withdrawal rate for etanercept. The ICERs were calculated using a 0.08 withdrawal rate, instead of a 0.08 annualised withdrawal rate [1-EXP(-0.08)].

Roche has therefore revised the estimated total cost, QALYs and ICERs derived from the analysis using the **un-pooled** and **pooled** TNF MTC response rates (excluding Moreland and Klareskog). Please find below a corrected version of tables 2 and 3 from our response to the 1st ACD along

with table 2 (also table 6) included in our response to the 2nd ACD. All changes compared to the original tables are underlined.

The corresponding excel version of the economic model generating these corrected results is also supplied for reference.

If you require any further clarification then please do not hesitate to contact us.

Yours Sincerely

Roche Response (ACD1) revised tables

Table 2: Cost effectiveness results utilising the revised ACR response rates of etanercept (MTC; anti-TNFs un-pooled)

		Submitted model	Revised MTC estimates (un-pooled)
Tocilizumab sequence	Total Direct Medical Cost (£)	100,485	103,331
	QALYs	8.95	9.075
Comparator sequence	Total Direct Medical Cost (£)	77,231	81,918
	QALYs	7.78	8.013
	ICER (direct medical costs, £ per QALY)	19,870	20,151

Table 3: Cost effectiveness results utilising the revised ACR response rates of etanercept (MTC; anti-TNFs pooled)

		Submitted model	Revised MTC estimates (pooled)
Tocilizumab sequence	Total Direct Medical Cost (£)	100,485	99,541
	QALYs	8.95	8.895
Comparator sequence	Total Direct Medical Cost (£)	77,231	76,818
	QALYs	7.78	7.756
	ICER (direct medical costs, £ per QALY)	19,870	19,949

Roche Response (ACD2) revised table

Table 1/6: Summary of economic model refinements and revised Roche cost effectiveness estimates

Model Assumption	Roche revised model – 2nd ACD – ICER – DMARD-IR	Roche revised model – 2nd ACD – ICER – TNF-IR
Roche base case	£19,870 per QALY	£22,003 per QALY
Using revised pooled MTC estimates	£19,949 per QALY	N/A
Withdrawal rate of etanercept used	£20,189 per QALY	N/A
Negative (3 years in DMARD-IR; 2.5 years in TNF-IR) and rebound effect (Back to baseline)	£22,003 per QALY	£22,876 per QALY
AE utility decrement equal to 0.05 per cycle	No Change	No Change
Administration cost equal to £154.3	£20,334 per QALY	£22,428 per QALY
Exponential long-tem HAQ modelling	£18,704 per QALY	£19,478 per QALY
Cumulative Impact of Changes (excl. exp LT HAQ modelling)	**£22,994 per QALY**	**£23,318 per QALY**