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BY E-MAIL

Dear Jeremy,

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

Thank you for the opportunity to review and comment on the technology assessment report.

Please find below our comments on the analysis performed by the assessment group. We have raised a number of points for consideration by the appraisal committee which we feel requires further discussion at the appraisal committee meeting.

Yours Sincerely

[redacted]

Points for consideration

There are a number of differences between the clinical and economic analyses submitted by Roche or reviewed by the assessment group and the conclusions contained within the assessment group report. We believe that these should be highlighted and that it is critical that the Appraisal Committee is aware of areas where Roche considers the assessment group's interpretation of the evidence may not be entirely consistent with the evidence considered.

Points 1 and 2 relate to the assessment of the clinical effectiveness where as points 3 and 4 are related with the results and conclusions drawn from the cost effectiveness analysis.

1. Evidence for TNF inhibitors as a class

The Assessment Report provides evidence for the effectiveness of TNF inhibitors either individually or as a class. In **5.3.4, TNF inhibitors as a class**, the section reports on studies that test the use of TNF-inhibitors after the failure of the first as a class. The report highlights a number of studies, including the Finckh Swiss Registry observational study. This is a robust study, the objective of which was to analyse the effectiveness of rituximab versus alternative TNF inhibitors on RA disease activity in different subgroups of patients; this design would seem well suited to address the decision problem in the MTA.

It was a prospective cohort study of RA patients who discontinued at least one TNF inhibitor and subsequently received either rituximab or an alternative TNF inhibitor, nested within the Swiss RA registry (SCQM-RA). The primary outcome, longitudinal improvement in DAS28, was analysed using multivariate regression models for longitudinal data and adjusted for potential confounders.

The Assessment Report states that, "Although Finckh was a non-randomized comparative study, the control arm was inappropriate for this section and as such the data from this are not considered." It is unclear to Roche why the Assessment Report considered this control arm inappropriate in this seemingly highly relevant study for this appraisal.

2. Statement of principle findings

In **Section 8 DISCUSSION,** and **8.1 Statement of principle findings,** the Assessment Report summarises the main points of the evidence. In **Section 8.1.9 Subgroup analyses**, the report correctly states that: "Evidence from the REFLEX trial suggested that the effectiveness of rituximab does not vary significantly according to reasons of withdrawal, baseline RF status and number of prior TNF inhibitors tried (one vs. more than one)."

However, further in the same section, the conclusion appears to contradict the evidence reviewed as it states, "Evidence from observational studies showed that …the proportion of patients who respond to a subsequent treatment (including TNF inhibitors, **rituximab**

and abatacept) decreases as the number of prior TNF inhibitor(s) that the patients have tried increases."

It is unclear to Roche whether the Assessment Report has given more weight to the REFLEX placebo-controlled RCT and agrees that the effectiveness of rituximab does not vary significantly according to number of prior TNF inhibitors tried (as presented by Roche in its original submission), or whether it has given more weight to the (unspecified) observational studies, which seem to demonstrate the opposite effect, and it remains unclear to Roche which evidence has been used to inform the latter.

3. Appropriate rituximab acquisition cost and impact to cost effectiveness

The Assessment Group has identified the cost of rituximab (per annum per patient) as an area of great uncertainty when rituximab is compared with the other treatments in this appraisal. Roche believe that given the results from both the Roche submission and the analysis performed by the assessment group, the uncertainty around the frequency of administration (from which the acquisition cost of rituximab is derived) has a minimal impact to the cost effectiveness analysis. This is has already comprehensively been evaluated and managed by Roche and the Assessment Group. The impact of the time-to-retreatment parameter to rituximab's cost effectiveness against all other biologics is best demonstrated in table 87 of the assessment report. Rituximab dominates or is highly cost effective against all other treatments when the shortest time-to-retreatment is used.

Roche demonstrated that the frequency of administration is consistently around 9 months. Several sources were utilised to determine the cost of rituximab. The latest market research data suggest that rituximab is given every 8.7 months on average (GfK HealthCare, January 200; Roche data on file). A further analysis of the extension trial retreatment data indicates that the time between treatments is even greater. The mean time to retreatment, taken from the extension study is 11.6 months (Roche analysis provided in original submission). Roche utilised the minimum time-to-retreatment frequency among the available sources to estimate the cost of rituximab that informed the base-case cost effectiveness analysis. Utilising the 8.7 months time-to-retreatment in the cost calculation the annual cost of rituximab is equal to ~£4,700 per patient. Utilising any other source in the calculation of the acquisition cost of rituximab should be coupled with the corresponding efficacy. Increasing time to re-treatment compared to that observed in the trial, with no adjustment to efficacy is will bias any analysis against rituximab.

In addition Roche provided a sensitivity analysis that varied the retreatment frequency from 6 to 12 months. It is important to note here that none of these 2 extreme values is expected to be observed consistently in routine clinical practice. Roche provided the sensitivity analysis to demonstrate that given a range of values and assumptions, rituximab remains the most cost effective therapy after the failure of an anti-TNF. If the extreme value of 6 months time-to-retreatment was considered as the basis of cost effectiveness analysis, rituximab's efficacy is expected to be different than the efficacy demonstrated in the trial given that the mean time-to-retreatment in the trial is substantially different.

4. Inconsistency in comparative effectiveness evidence of rituximab compared to abatacept and assessment group health economic model outcomes

Table 83 of the assessment group's report suggest that abatacept is more effective than rituximab (mean QALYs gained in rituximab strategy **3.10** compared to **3.28** for abatacept treatment strategy). It is unclear how this additional benefit is generated in favour of abatacept. Roche performed an indirect comparison of the 2 therapies being the only therapies in this appraisal with phase III RCT data. In the Roche indirect comparison provided (ref if published?) rituximab is more effective than abatacept across all 3 ACR categories (ACR 20: 46% vs 43%, ACR 50: 23% vs 22% ACR 70: 14% vs 8%; rituximab first).

Echoing this analysis the assessment group performed an indirect comparison, comparing the 2 therapies and found similar differences in effectiveness. Table 46 (section 5.6.2) of the assessment report shows that the relative risks (RR) when comparing the 2 therapies favour rituximab in the ACR 20 (RR: 1.115; CIs 0.677 1.836) and ACR 70 (RR: 1.798; CIs 0.242 13.350) categories while there was no difference found in the ACR 50 category.

Therefore it is unclear how this efficacy advantage for rituximab reported by both Roche and the assessment group is translated to less QALYs gained by the RTX treatment strategy compared to the abatacept treatment strategy.

The final scope of this appraisal and the written confirmation obtained from the response to Roche's comments on the draft scope strictly prohibits the evaluation of multiple biologic treatment strategies following the failure of the 2nd bDMARD. Whilst Roche and the Assessment Group have complied to the scope we believe that failure to evaluate such scenarios represents a missed opportunity to further advance the chronic management of rheumatoid arthritis.