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BY EMAIL

2nd April 2015

RE: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis [ID537]

Dear Meindert,

Thank you for giving us the opportunity to comment on the report prepared by the Decision Support Unit (DSU) for this appraisal. Following our review of this report, in combination with the earlier work performed by the Assessment Group (AG), we remain in complete disagreement with the conclusion that the available evidence on HAQ progression suggests a lower overall rate of disease worsening than that assumed in previous cost-effectiveness analyses. While the DSU report is thorough, we believe the only conclusion which could be made is that there is limited evidence to generate robust estimates on the rate of long term HAQ progression for patients with moderate to severe rheumatoid arthritis (RA).

As previously stated following the original AG report, we believe that the evidence identified by the DSU does not adequately reflect the patients being considered as part of the NICE appraisal [ID537]. In most of the datasets, patients have been identified with early RA and not moderate to severe RA, therefore we are not confident that the conclusions drawn from these datasets are relevant for this appraisal.

Our response has focused on the following key areas within the DSU Report:

- Attrition observed in the registries

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- Generalisability of the registry data to UK patients

Yours sincerely,

[redacted]

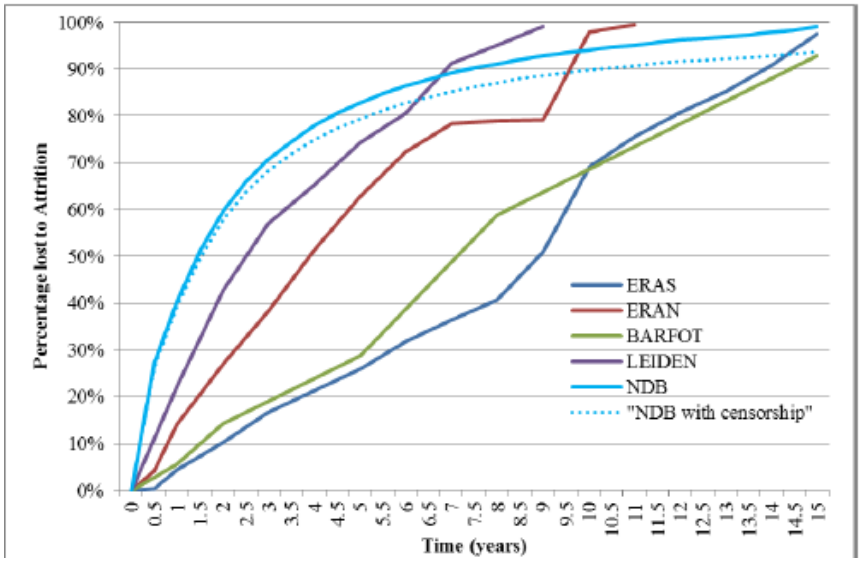
[redacted], [redacted]

Roche Products Limited

Attrition of patients lost in the registries

As highlighted throughout the DSU report, the registries have a significant weakness when used as part of the evidence base for assessing biologic treatments for RA due to their large dropout rates. While this is to be expected in a longitudinal study, the high attrition rates are likely to impact any assessment of long term HAQ progression. As the discussion on the methods used in this appraisal has focused on HAQ scores in the long term, when considering these high attrition rates (at best, 40% at 8 years in the case of the ERAS study) we do not believe the reported data offer anything new to this assessment.

Figure 1: Attrition rates of registries used in the DSU report



Generalisability of the registry data to UK patients

As previously stated, Roche are deeply concerned that the evidence in the identified registries does not adequately match UK patients with moderate to severe RA. Rheumatologists consulted by Roche do not believe the evidence within the DSU report reflects UK patients who would be considered for biologic treatment.

A comparison of the baseline characteristics from the British Society for Rheumatology Biologics Register (BSRBR; Table 1 below) with the registries described by the DSU (Table 2) shows significant difference in the patient characteristics. For example, there is a large disparity in the mean disease duration and the mean HAQ scores. These two parameters are key drivers in the assessment of long term HAQ progression, and it is not clear that the DSU has been able to adjust

for these differences in their statistical analysis, nor how such an adjustment could be validated.

We strongly disagree with the DSU that the results of their report are generalisable to UK patients eligible for biologic therapy, and therefore believe they cannot be used within the base case cost-effectiveness model.

Table 1: Patient subgroup characteristics for use in cost-effectiveness analysis

	i) BSRBR		ii) Severe		iii) Moderate	
	Mean	SD (%)	Mean	SD (%)	Mean	SD (%)
Age	56.2	12.2	57.3	12.5	58.0	13.6
Proportion female	0.8	0.4	0.8	0.2	0.7	0.2
Disease duration (yrs)	13.3	9.6	9.4	9.3	10.2	10.5
DAS28	6.6	1.0	6.2	0.8	4.4	0.6
Previous DMARDSs	3.9	1.6	2.8	1.0	2.9	1.0
HAQ	2.0	0.6	1.6	0.7	1.5	0.8
Weight (kg)	73.1	17.6	78.8	19.6	76.1	19.1

Table 2: Baseline characteristics of patients included in the registries identified by the DSU

	Mean (standard deviation)				
	ERAN	ERAS	LEIDEN	BARFOT	NDB
HAQ Observations	1091	1421	498	2455	19,292
Age	56.72 (13.85)	55.13 (14.37)	55.82 (16.07)	58.06 (15.73)	58.88 (13.38)
Gender	0.3190 (0.4663)	0.3329 (0.4714)	0.3173 (0.4659)	0.3308 (0.4706)	0.2205 (0.4146)
HAQ	1.085 (0.7692)	1.143 (0.7653)	1.020 (0.7113)	1.032 (0.6542)	1.041 (0.7257)
DAS	4.561 (1.575)	4.501 (1.057)	4.806 (1.064)	5.261 (1.235)	-
RADAI	-	-	-	-	2.875 (1.652)
Disease duration (months)	8.403 (6.920)	8.167 (6.077)	-	5.997 (3.089)	12.26 (11.26)
ACR fulfilment for RA	0.5263 (0.4995)	0.7023 (0.4574)	*	*	-
Positive Rheumatoid Factor	0.6257 (0.4842)	0.6306 (0.4828)	-	-	-
Failed two DMARDs	0.0110 (0.1043)	0 (-)	-	-	0.3118 (0.4632)

*Fulfilment of 1987 ACR criteria for RA was a requirement for entry to these studies