**Golimumab in the Treatment of Rheumatoid Arthritis**
**NICE STA Clarification Questions 2**

1) Section 6.3.1, Page 129. The trial by Kay et al. (2008) was used in the meta-analyses (as stated in Tables 18 and 19, pages 60-61) and in the mixed treatment comparison analysis (as stated in Table 54, pages 77-78) for the DMARD population. However, Section 6.3.1 states that only the GO-FORWARD and GO-AFTER trials were used for the clinical efficacy parameters in the cost-effectiveness analysis. Please clarify whether the Kay et al. (2008) trial was used in the cost-effectiveness analysis. If this trial was not used in the cost-effectiveness analysis, please provide a justification for this exclusion.

Kay et al and GO-FORWARD were included within the meta-analyses and MTC for the DMARD experienced population. These outputs were included within the 'Indirect Comparison' worksheet. There is an inconsistency within the 'First Line Efficacy' worksheet of the model. The transition probabilities were originally calculated based upon only the GO-FORWARD responders. This has been updated in the model with the below figures (ie, the absolute patient numbers from GO-FORWARD were added to the absolute patient numbers for Kay et al).

| | Golimumab 50mg | | Placebo | |
|---|---|---|---|---|
| | No. | Sample | No. | Sample |
| **ACR 20** | 53+26 = 79 | 89+35 = 124 | 37+16 = 53 | 133+35 = 168 |
| **ACR 50** | 33+14 = 47 | 89+35 = 124 | 18+4 = 22 | 133+35 = 168 |
| **Dropout** | 2+2 = 4 | 89+35 = 124 | 6+3 = 9 | 133+35 = 168 |

The base case ICERs, as presented in the first set of clarification questions (which included updated unit costs) is reproduced below for reference.

| **Technologies** | **Total costs (£)** | **Total QALYs** | **Incremental costs (£)** | **Incremental QALYs** | **ICER (£) versus Baseline (Methotrexate)** | **Incremental analysis** |
|---|---|---|---|---|---|---|
| **Methotrexate** | £39,589 | 4.569 | - | - | - | - |
| **Adalimumab** | £70,376 | 5.792 | £30,787 | 1.223 | £25,211 | £25,211 |
| **Golimumab** | £71,229 | 5.827 | £853 | 0.035 | £25,193 | £24,371 |
| **Infliximab** | £75,904 | 5.651 | £4,675 | -0.176 | £33,628 | Dominated |
| **Certolizumab** | £76,868 | 5.768 | £964 | 0.117 | £31,086 | £8,239 |
| **Etanercept** | £77,548 | 6.133 | £680 | 0.365 | £24,301 | £1,863 |

The inclusion of Kay et al in the calculations of the transition probabilities (within the 'First Line Efficacy' worksheet) produces the below results, which are quite similar to the base case results presented in the above table.

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) versus Baseline (Methotrexate) | Incremental analysis |
|---|---|---|---|---|---|---|
| **Methotrexate** | £39,161 | 4.619 | - | - | - | - |
| **Adalimumab** | £71,467 | 5.845 | £32,306 | 1.226 | £26,370 | £26,351 |
| **Golimumab** | £73,082 | 5.923 | £1,615 | 0.078 | £26,024 | £20,705 |
| **Infliximab** | £76,659 | 5.691 | £3,577 | -0.232 | £34,990 | Dominated |
| **Certolizumab** | £77,296 | 5.775 | £637 | 0.084 | £32,992 | £7,583 |
| **Etanercept** | £79,579 | 6.235 | £2,283 | 0.460 | £25,022 | £4,963 |

2) Clarification responses Question A10, Page 17. Table 20 of the clarification responses lists a number of adverse events trials as being 'included.' However, it is unclear how these trials were included in the assessment. Please state clearly how these identified adverse events trials were used in the assessment. Please also provide details of the study drug(s) and study design of these trials.

'Included' within Table 20 of the clarification response means these trials were not immediately excluded and thus were reviewed for relevant safety data (serious adverse events, serious infections, injection site reactions and discontinuations). No trials which primarily assessed the safety outcomes of the interventions were found which were not already identified from the clinical systematic review presented in Section 5.2 of the MS.

3) Section 5.8., Page 86 onwards. For all adverse events meta-analyses please state at what time point the outcomes are reported (eg. at 24 weeks?)

The latest time point for all safety parameters was extracted for each trial. The latest time point for the vast majority of the trials was 24 weeks. The below table presents the time points for those trials which presented earlier or later time points across the safety parameters. Data for these time points (across all available safety parameters) were extracted and included within the economic evaluation.

| Product | Study | Safety time point |
|---|---|---|
| ADA | Chen 2009 | 12 weeks |
| ADA | DE019 | 12 months |
| CTZ | RAPID 1 | 12 months |
| ETN | TEMPO | 12 months |

| | | |
|---|---|---|
| GOL | Kay 2008 | 16 weeks |
| IFX | ATTEST | 12 months |
| IFX | ATTRACT | 12 months |
| IFX | Abe 2006 | 14 weeks |
| IFX | START | 12 months |

4) Clarification responses Question A35, Page 42. Please clarify in full the handling of data from:
i) patients who received rescue/early escape therapy and crossover therapy in the GO-FORWARD and GO-AFTER studies
ii) patients who received infliximab crossover therapy in the Kay et al. trial.

(Patients within GO-FORWARD and GO-AFTER may be counted more than once due to cross over or early escape at Week 16 as the modelling time point is at Week 24 due to resource use schedules within the UK (based on clinical expert opinion). All time points for Kay et al were extracted at week 16 (primary endpoint and the latest time point for ACR response figures reported in the publication). There was therefore no need to take into account crossover therapy which occurred from Week 20 onwards.

5) Section 5.3.7, Page 57. The MS states in the clinical effectiveness section: 'For golimumab, subgroup analyses were conducted based on demographic features, geographic region, baseline disease characteristics, and baseline medications for RA in GO-FORWARD and GO-AFTER trials...Separate post-hoc analyses were conducted comparing individual golimumab doses with placebo on some of the baseline demographics and disease characteristics.' Please state the location (section and page number) of the description and results of each of these subgroup analyses in the MS.

The above description which was presented in Section 5.3.7, Page 57 is part of the clinical write-up for the overall GO-FORWARD and GO-AFTER study design which was undertaken by the investigators. Information in this detail was not included within the MS but was described for reference of the protocol study design in which the clinical study reported was based upon.

[redacted]

6) Section 5.6 and Appendix 17. The report states that when estimating the relative risks (RRs) for ACR20 in the mixed treatment comparison, the numbers achieving ACR 20 were estimated by taking the ACR50 responders away to identify the group who were exclusively ACR20 responders. However the source code in Appendix 17 suggests that this has not been undertaken. Please can you clarify if the source code in Appendix 17 is

correct and whether the RRs for ACR20 are for only those patients who were an ACR20 and not an ACR50 responder.

Section 5.6 within the clinical effectiveness section presents the risk ratios but does not discuss 'double counting' of ACR20 and ACR50 methods. Methods of subtracting ACR50 responders from the ACR20 responders is detailed within the cost-effectiveness Section 6.3. The adjustment to the risk ratios occurs after the meta-analyses and MTCs were conducted and therefore not reflected within the source code (Appendix 17). The 'First Line Efficacy' worksheet of the model includes tagged comments to show the methods of subtracting ACR50 responders from ACR50 (e.g. in cells D38:F50).