Abbott's response to the Appraisal Consultation Document (ACD) of golimumab for psoriatic arthritis

Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the appraisal of golimumab for the treatment of psoriatic arthritis. Abbott's comments are set out under section headings containing the questions NICE asks stakeholders to comment on for the ACD.

1. Do you consider that all of the relevant evidence has been taken into account?

1.1 Modelling of results to include patients requiring the 100mg golimumab dose

The marketing authorisation for golimumab states that, "*in patients weighing more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered*." However, no modelling was undertaken that included a proportion of patients weighing more than 100kg requiring the 100mg dose. This was the case even following a request from the ERG to provide a sensitivity analysis with the relevant proportion of the cohort on this higher dose with corresponding costs. Given that the higher dose is double the cost of the 50mg dose, Abbott considers that there should be some explicit wording around the use of the 100mg dose, particularly if the preliminary recommendations in the ACD change.

In a European study evaluating the real world use of adalimumab in psoriatic arthritis patients (STEREO)[1], 17.27% of the 440 patients enrolled weighed 100kg or more. Therefore, Abbott suggests that additional modelling be undertaken to explore the cost-effectiveness of golimumab including a percentage of patients receiving the higher golimumab dose as per the ERG's request i.e. the annual drug acquisition cost of golimumab should be weighted to include a range of patients requiring the higher dose to see the impact this has on the ICERs vs. standard care and the other anti-TNFs.

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?

In section 3.11 of the ACD, the Committee noted that "*Of the four TNF inhibitors, golimumab had the lowest HAQ score change from baseline, both in participants whose disease responded to treatment based on PsARC score and those whose disease did not respond.*" Furthermore, in section 4.7 of the ACD it states "*The Committee inferred that, based on the changes in HAQ score, golimumab and etanercept could not be assumed to be of equal efficacy*." Abbott contends that the smaller improvements in the HAQ score reported for golimumab are inextricably linked to its radiographic progression data.

2.1 It has not been shown conclusively that golimumab inhibits structural joint damage

There were two co-primary endpoints hypothesised in the statistical analysis of the golimumab PsA trial: 1) the percentage of ACR20 responders at week 14, and 2) the change from baseline in PsA modified van der Heijde-Sharp (vdH-S) score at Week 24[2].

Interestingly, the results for the second co-primary endpoint were not published in the Arthritis & Rheumatism paper discussing the 24 week efficacy and safety results[3]; and neither were they submitted to the EMEA in the application for marketing authorisation: "*Data for the co-primary endpoint of change from baseline in PsA modified van der Heijde-Sharp (vdH-S) score at Week 24 were not provided in this application*." (Page 40 of the Scientific discussion from the EPAR for Simponi)[2].

Following a request from the ERG, the manufacturer provided the 24 week joint damage data. Results showed that the baseline vdH-S score for the 50mg golimumab group improved by -0.16 compared to a 0.27 worsening in the placebo group (p=0.01); and there were no statistically significant differences in the vdH-S score between the golimumab 100mg arm and placebo at week 24. These data suggest

that golimumab has minimal impact in preventing joint damage. These findings are not consistent with those observed for the other three anti-TNFs.

The GO-REVEAL golimumab trial used the vdH-S score to evaluate radiographic changes in the joints, this was the same scoring tool used in the infliximab trials. At week 24 in IMPACT 2, the mean improvement in the total baseline vdH-S score from baseline in the infliximab 5mg/kg group was -0.7 compared to a worsening of 0.8 in the placebo group ($p<0.001$ for the comparison)[4]. The mean baseline vdH-S score was slightly worse in the infliximab trial (30.3 ± 61.4 for infliximab 5mg/kg vs. 23.85 ± 35.41 for golimumab 50mg), however the difference in improvement from baseline between the two anti-TNFs is still four-fold.

Although the adalimumab and etanercept PsA trials used a different scoring tool to calculate radiographic changes in the joints, both anti-TNFs showed highly statistically significant differences in the modified total Sharp score at week 24 compared to placebo ($p<0.001$)[5,6].

The radiographic data from the phase III trials of adalimumab, etanercept and infliximab resulted in the inclusion of specific wording in the licence to reflect this benefit. For example in the therapeutic indication section of the adalimumab SmPC it states: "…*Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function"*.[7] There is no such wording in the golimumab SmPC as the manufacturer did not include the radiographic data for golimumab in its regulatory application.

Interestingly, the apparent inability of golimumab to prevent structural joint damage has also been observed in the rheumatoid arthritis data. In the marketing authorisations for adalimumab, etanercept and infliximab there is explicit wording highlighting that the rate of progression of joint damage as measured by X-ray is reduced, whereas there isn't such a claim in the golimumab RA licence. This is because results from the GO-FORWARD study evaluating golimumab in RA patients who have had an inadequate response to methotrexate showed that there was no significant reduction in disease progression in patients with established RA receiving 50mg golimumab. There was some discussion that the trial population in the GO-FORWARD study seemed to be at a lesser risk of radiographic progression as the baseline characteristics of these patients were less severe than have previously been reported for the other anti-TNF trials; however there was still no difference in the mean change from baseline in the vdH-S score between the 50mg golimumab + methotrexate group and the placebo + methotrexate group at 24 weeks, 0.55 and 0.6, respectively.[8]

In summary, although golimumab controls the signs and symptoms of PsA as measured by ACR and PASI with similar efficacy to adalimumab, etanercept and infliximab; it has not demonstrated that it inhibits structural joint damage in the same way the other anti-TNFs do. It can therefore not be considered to have the same efficacy as adalimumab, etanercept and infliximab. Consequently, all the long-term benefits relating to preventing joint damage, captured in the model by assuming zero HAQ progression, should not be assumed for golimumab as there is currently little evidence to support this.

2.2 Possible rationale as to why golimumab has not been shown to prevent joint damage

The European Medicines Agency discussed the rationale for the chosen doses of golimumab in the phase III clinical trial programme, 50 mg and 100mg every 4th week. The Agency concluded that the rationale for the choice was "*not fully obvious*" (Page 63 of the EPAR). Abbott suggests that the interval between doses of golimumab is too great to maintain tight disease control. This is evidenced by data in the EPAR discussion on serum trough levels of golimumab (outlined below). As a consequence patients are not achieving adequate control of their underlying disease, which may explain the lack of data showing that golimumab inhibits radiographic progression in both PsA and RA.

On page 19 of the EPAR it discusses the pharmacokinetic data for golimumab. In most golimumab studies, serum concentrations of golimumab were measured using the sandwich ECLIA assay. The lower limit of quantification (LLOQ) of this assay was 200 ng/ml with an MRD (minimum required dilution) of 10, however, the EPAR notes that this limit was not low enough to estimate trough concentrations in all subjects following the administration of 50 mg every 4 weeks (q4w). In other words, even with a very low level of quantification to detect serum concentrations of golimumab,

following the administration of 40mg every 4 weeks it was still not possible to detect trough concentrations in some patients.

Furthermore, the EPAR notes on page 20 that, "*median serum trough concentrations obtained over longer time periods indicate a tendency toward a decrease over time [up to 52 weeks], which may be related to increased formation of antibodies toward golimumab and possibly an increased risk of inefficacy."*

Interestingly, as the LLOQ of the detection assay was not low enough to estimate trough concentrations in all subjects the observed median values may also be upward biased (EPAR, page 20). This coupled with a tendency toward a decrease over time suggests that serum levels of golimumab are too low when it is administered once every 4 weeks.

The posology for golimumab states that it should be given once monthly, and not once every 4 weeks. This is because although dosing was scheduled at 4-week intervals, a 3 to 7 day dose window was specified in the protocol allowing for 30 to 31 day intervals if necessary. Abbott could not determine how many subjects made use of the 3 to 7 day window, and therefore does not know how many patients received golimumab less frequently than once every four weeks. However, if in some subjects serum trough levels of golimumab were not detectable following the administration of 50 mg every 4 weeks, it is a concern that an increased interval between doses will have serious implications for disease control.

If a more frequent dosing regimen was implemented for golimumab, it is possible that the underlying disease would be better controlled, which would be supported by evidence of inhibition of radiographic progression. However, such a dosing regimen would have a substantial effect on the cost-effectiveness estimates.

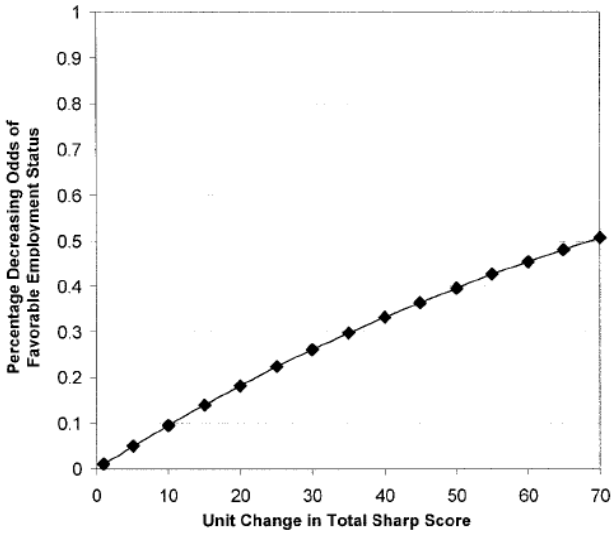
2.3 Correlation between joint damage measured by X-ray and HAQ

The importance of inhibition of radiographic progression is becoming increasingly apparent across all of the rheumatological diseases, with studies in rheumatoid arthritis having demonstrated that inhibition of radiographic progression has a meaningful impact on patients' lives in terms of both HAQ scores and employment status.

Using data from an RCT of etanercept + methotrexate in patients with rheumatoid arthritis, van der Heijde *et al.* found that after adjusting for age, sex and disease activity, HAQ scores were significantly determined by both the absolute level of joint damage and the radiographic progression[9]. The authors concluded that patients with greater radiographic damage, and those with recent radiographic progression, have a higher degree of disability.

In a similar vein, analysis of data from an RCT of adalimumab + methotrexate in patients with RA found that radiographic progression was significantly correlated with employment status, indicating that this measure of disease has a direct impact on the patient[10]. Figure 2.3 from the van Vollenhoven study shows the relationship between increasing joint damage measured by the Sharp score and the percentage of decreasing odds of gaining/maintaining favourable employment.

Figure 2.3: Relationship between worsening joint damage and the odds of being in employment



2.4 Confusion around the HAQ changes from baseline in manufacturer's submission at weeks 14 and 24

On page 69 of the manufacturer's submission (MS), the mean change in HAQ score from baseline was presented for weeks 14 and 24. Table 2.4 reproduces the numbers from the MS below:

Time point	Golimumab 50mg	Placebo
14 weeks	0.3	0.4
24 weeks	0.3	-0.03

Abbott is unclear as to how to interpret these numbers. Given that the HAQ score ranges from 0 to 3, where 0 is equal to no disability and 3 equates to severe disability, improvements in HAQ are usually presented in the negative. If we assume that this convention has been reversed and that there is a 0.3 improvement at week 14 in the golimumab arm as opposed to a worsening, it appears that patients receiving placebo had a better improvement in their HAQ score then those patients receiving golimumab. Since this time point is before the early escape option at week 16 this presumably includes all patients in the placebo arm, including non-responders.

If the week 14 placebo HAQ change is correct, then patients worsen considerably in just 10 weeks for the week 24 mean HAQ change from baseline to be -0.03. Given that changes in HAQ are key in the economic modelling, these numbers should be checked and amended as necessary in any subsequent analyses.

2.4 Estimation of nurse time required to teach subcutaneous administration

In the manufacturer's submission, the cost of an additional 4 hours of nurse time was added on top of the outpatient visit to train patients to self-administer an anti-TNF. This cost was applied to all the subcutaneous agents: adalimumab, etanercept and golimumab. Abbott contends that this is a gross overestimation of the time taken to train patients to self-administer. In NICE clinical guidelines and costing templates of subcutaneously administered agents, the cost of a one hour training session with a Band 6 nurse has been used routinely for the time taken to train patients to self-administer with an injectable pen.

Furthermore, for patients receiving adalimumab nurse training to teach self-injection is provided free of charge as part of the home delivery package.

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?

There is no conclusive evidence to show that golimumab prevents the progressive joint damage associated with psoriatic arthritis. Evidence shows that there is a correlation between radiographic progression and functional disability, plus other hard outcomes such as employment status. Given that the other anti-TNFs for PsA have demonstrated an ability to prevent progressive joint damage and therefore long-term functional disability, Abbott can understand why the Committee has made its preliminary recommendations for golimumab.

4. 4. Are there any equality related issues that may need special consideration?

None that Abbott is aware of.

References

[1] Clinical Study Report M04-724 (STEREO) - adalimumab for the treatment of psoriatic arthritis. Abbott Laboratories. Data on File.

[2] European Medicines Agency Assessment Report for Simponi (EPAR). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000992/WC500052372.pdf. Last accessed 19 October 2010.

[3] Kavanaugh A, McInnes I, mease P, Krueger G, Gladman D, Gomes-Reino J *et al.* Golimumab, a New Human Tumor Necrosis Factor _ Antibody, Administered Every Four Weeks as a Subcutaneous Injection in Psoriatic Arthritis. *Arthritis & Rheumatism* 2009;**60**(4):976-986.

[4] van der Heijde D, Kavanaugh A, Gladman D, Antoni C, Krueger G, Guzzo C *et al.* Infliximab Inhibits Progression of Radiographic Damage in Patients With Active Psoriatic Arthritis Through One Year of Treatment. *Arthritis & Rheumatism* 2007;**56**(8):2698-2707.

[5] Mease P, Gladman D, Ritchlin C, ruderman E, Steinfield S, Choy E *et al*. Adalimumab for the Treatment of Patients With Moderately to Severely Active Psoriatic Arthritis. *Arthritis & Rheumatism* 2005;**52**(10):3279-3289.

[6] Mease P, Kivitz A, Burch F, seigal E, cohen S, Ory P. Etanercept Treatment of Psoriatic Arthritis - Safety, Efficacy, and Effect on Disease Progression. *Arthritis & Rheumatism* 2004;**50**(7):2264-2272.

[7] Summary of Product Characteristics (SmPC) of adalimumab (HUMIRA). The electronic Medicines Compendium (eMC). http://www.medicines.org.uk/EMC/medicine/21201/SPC/Humira+Pen+and+Syringe/. Last accessed 19 October 2010.

[8] Emery P, Fleischmannz R, van der Heijde D, Keystone E, Genovese M, Conaghans G. Golimumab and Radiographic Progression in Rheumatoid Arthritis: Results of GO-BEFORE and GO-FORWARD Studies. *American College of Rheumatology Annual Congress* 2009. http://acr.confex.com/data/abstract/acr/2009/Paper_16308_abstract_11186_0.jpg

[9] Van der Heijde D, Landewe R, van Vollenhoven R, Fatenejad S, Klareskog L. Level of radiographic damage and radiographic progression are determinants of physical trial function: a longitudinal analysis of the TEMPO trial. *Annals of Rheumatic Disease* 2008;**67**:1267-1270.

[10] Van Vollenhoven, Cifaldi M, Ray S, Chen N, Weisman M. Improvement in Work Place and Household Productivity for Patients With Early Rheumatoid Arthritis Treated With Adalimumab Plus Methotrexate: Work Outcomes and Their Correlations With Clinical and Radiographic Measures From a Randomized Controlled Trial Companion Study. *Arthritis & Care research* 2010;**62**(2):226-234.