NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233) [ID694]

19th June 2015

UCB Response to Appraisal Consultation Document

UCB Response to ACD

UCB welcomes the opportunity to respond to the appraisal consultation document (ACD) from the first Committee meeting for the multiple technology appraisal (MTA) on the use of anti-TNFs in ankylosing spondylitis (AS) and axial spondyloarthritis without the radiographic evidence of AS (nr-axSpA).

Following a review of the report we would like to provide a number of comments and observations for consideration by the NICE committee. These comments are structured into two key sections:

(1) Comments related to certolizumab pegol, such as details of the approved Patient Access Scheme (PAS) and clarification of the RAPID-axSpA study design, particularly how inclusion of comparable numbers of patients with AS and nr-axSpA was per study protocol and unique feature of this study, allowing direct comparisons of baseline patient burden and treatment response across the spectrum of axial spondyloarthritis (axSpA);
(2) General responses to the ACD report, including the patient need for sequential use of anti-TNFs in axSpA and the importance of extra-articular manifestations for patients living with axSpA.

1 Comments related to certolizumab pegol

1.1 Certolizumab pegol PAS

We welcome the ACD 1 preliminary recommendation for certolizumab pegol without the PAS. UCB understands that the ACD should be a reflection of the first Committee meeting and at the time of the meeting, the PAS for certolizumab pegol was under consideration by the Department of Health and therefore, the PAS was not considered within the Committee's preliminary recommendations.

For the purpose of ACD 2, we would like to inform the Committee that the PAS for certolizumab pegol in axSpA has now been approved and is identical to the PAS already in place for rheumatoid arthritis; that is the first 12 weeks of treatment (ie. the first 10 vials) are provided at zero cost to the NHS.

We would like to flag that the following sections of the ACD, mentioning the certolizumab pegol PAS, are affected and suggest they be updated accordingly as part of ACD 2/FAD:

- Section 1.1 and Section 1.3: suggest the text indicate that "*certolizumab pegol is recommended with or without a patient access scheme, where the first 12 weeks (10 pre-loaded 200 mg certolizumab pegol syringes) are provided at zero cost to all patients starting treatment*".
- Section 3.9: suggest the annual acquisition costs of certolizumab pegol be updated to reflect the agreed PAS. More precisely, suggest the text indicate that "*Assuming the recommended dosage is followed (see section 3.7), the annual cost for the first year of treatment with certolizumab pegol is estimated at £10,367.50, reduced to £6,792.50 (including the agreed patient access scheme); for the maintenance year the cost of treatment is estimated at £9,295.*"
- Section 4.36: suggest the text be updated in the final guidance, stating that the certolizumab pegol costs with and without the PAS were considered.
- Sections 4.39 – 4.44, within the table on p.37–40: suggest the base case results for certolizumab pegol be changed to be the one including the PAS.
- Section 5.4: suggest the certolizumab pegol PAS also be described in Section 5.4 and in the table on p.70.

1.2 Certolizumab pegol Summary of Product Characteristics

In Section 3.7, p.9, it is stated that "*The recommended induction dosage [for certolizumab pegol] for patients with ankylosing spondylitis…*". In the summary of product characteristics (SPC) for certolizumab pegol, this initial dose is referred to as a "*loading*" dose, rather than an "*induction*" dose.[1] UCB therefore request that the word "*induction*" is changed to "*loading*", to accurately reflect the SPC.

In Section 3.8, "*autoimmune conditions (including lupus-like syndrome)*" is listed as an adverse reaction associated with certolizumab pegol treatment. The SPC for certolizumab pegol does not list autoimmune conditions as an adverse reaction, but rather it is stated that, "*the impact of long-term treatment with Cimzia on the development of autoimmune diseases is unknown*" and that, "*there have*

been rare reports of other immune-mediated conditions; the causal relationship to Cimzia is not known".[1] Lupus-like syndrome is listed as the only auto-immune disorder that has been associated with certolizumab pegol treatment and therefore we suggest the wording of the ACD in Section 3.8 be changed to list only lupus-like syndrome, rather than other autoimmune conditions.

1.3 Description of the RAPID-axSpA trial

1.3.1 Recruitment of patients across the axSpA spectrum

Section 4.17 states: "*The Assessment Group reported issues with 2 of the trials in nonradiographic axial spondyloarthritis (ABILITY-1 for adalimumab and Rapid-axSpA for certolizumab pegol), which were highlighted by the US Food and Drug Administration. These 2 trials included large proportions of people with ankylosing spondylitis.*"

UCB would propose rewording Section 4.17 to the following: "*The Assessment Group reported issues with 2 of the trials in non-radiographic axial spondyloarthritis (ABILITY-1 for adalimumab and Rapid-axSpA for certolizumab pegol), which were highlighted by the US Food and Drug Administration. These 2 trials were found to have discrepancy in classification of patients with non-radiographic axial spondyloarthritis or ankylosing spondylitis between local classification and central readings of X-rays. This was found to have an overestimation of the treatment benefit observed with TNF-alpha inhibitors in 1 of the trials (ABILITY-1). Rapid-axSpA was designed to include patients with ankylosing spondylitis or non-radiographic axial spondyloarthritis; misclassification did not impact the Rapid-axSpA study results, with similar treatment effect regardless of how patients were classified.*"

UCB considers the wording in the above mentioned section to be misleading in relation to the RAPID-axSpA trial. The RAPID-axSpA trial was designed to examine the efficacy of certolizumab pegol across the spectrum of patients with active axSpA, including both AS and nr-axSpA sub-populations. To enter the study patients had to have a physician diagnosis of axSpA, meet the ASAS classification criteria and have active disease plus the presence of objective signs of inflammation despite current treatment with NSAIDs, ie. the study recruited a cohort reflecting the label population. Recruited patients were then stratified into the AS and nr-axSpA subpopulations using the modified New York (mNY) criteria to ensure balance between the subgroups in each treatment arm. It is therefore misleading to state that the RAPID-axSpA study included a large proportion of AS patients when this group was recruited as per study protocol.

As with historic AS registration studies, patients in the RAPID-axSpA trial were classified by a local investigator since this reflects how patients are diagnosed in clinical practice. A protocol amendment was later made to the study to conduct baseline X-rays of the sacroiliac joints, which were read centrally, to allow for an assessment of disease progression from nr-axSpA to AS to be performed at the end of the study. A discrepancy in classification of patients between the local investigator and central readers was found in the RAPID-axSpA study, with some patients classified as AS being reclassified as nr-axSpA and some nr-axSpA patients being reclassified as AS. However, this is a well-known phenomenon, reflects the unreliability of X-rays for classification and diagnosis, and is consistent with literature reports that also show a high degree of discrepancy between readers.[2]. Importantly, regardless of how patients were classified (by local investigators or according to the central read), the US Food and Drug Administration concluded that the treatment effect was the same, with the likelihood of achieving the primary endpoint of ASAS20 response not being dependent on whether patients had definitive evidence of sacroiliitis on X-ray.[3]

In light of this clarification, UCB feels that the above revised wording better reflects the differences in design of the 2 trials and the context of the analysis performed by the US Food and Drug Administration.

1.3.2 Objective signs of inflammation

In Section 4.58, it was stated: "*The Committee noted comments from the Assessment Group that heterogeneity across the trials of nonradiographic axial spondyloarthritis may have confounded the outcomes for TNF-alpha inhibitors. The Committee heard from the clinical experts that these trials included people who were less likely to benefit from TNF-alpha inhibitors (people without objective signs of inflammation such as MRI changes and elevated C-reactive protein, for whom TNF-alpha inhibitors are not indicated according to their UK marketing authorisations*".

UCB considers that this statement is misleading, suggesting that all trials recruited some patients without objective signs of inflammation. UCB would like to clarify that the RAPID-axSpA trial recruited patients as per the UK marketing authorisation, that is, both AS and nr-axSpA patients had objective signs of inflammation, as determined by an elevated CRP measure or as detected by MRI.[4] Patients with AS and nr-axSpA had comparable high disease burden at baseline and demonstrated a similar treatment response to certolizumab pegol. UCB requests that the statement be revised to specifically highlight those trials that did include patients without objective signs of information.

1.4 Re-clarification of reporting of adverse events for anti-TNFs

In Section 4.21 it is stated: "*When individual TNF-alpha inhibitors were analysed separately, only infliximab and certolizumab pegol were associated with statistically significant increases in adverse events compared with control treatments… certolizumab pegol was associated with higher rates of serious infections (NNH 12, 95% CrI 4 to 79) and serious adverse events (NNH 18, 95% CrI 9 to 162).*"

These conclusions are made with little context provided and make no mention of the limitations associated with the Cochrane review.

The authors of the Cochrane meta-analysis acknowledge several limitations of their meta-analysis. Their findings are based on indirect comparisons and should be interpreted with caution because trials differed in patient populations, prior failed therapies, concomitant use of DMARDs, trial duration, and dose of biological; and event rates were often low.[5]

UCB request that additional context is added when the results of independent meta-analyses such as the Cochrane review are summarised, and refer to the limitations inherent in such analyses.

Long-term safety of certolizumab pegol in axSpA has been shown to be consistent with other agents in this class. The absolute rate of serious infection events for patients treated with certolizumab pegol was similar to observations from other studies, which has been confirmed in a comprehensive pooled safety analysis including over 4,000 patients with rheumatoid arthritis, with over 9,000 patient years of follow up.[6] Furthermore, the EPAR for certolizumab pegol states that in the RAPID-axSpA study, the adverse event profile of certolizumab pegol was as expected for TNF alpha inhibitors and consistent with previous experience for certolizumab pegol. No new safety signals were identified.

Given the evidence highlighted above, UCB would request that additional context is provided to safety analyses, such as the Cochrane review, to provide a balanced and objective account of the safety profile of all agents.

1.5 Molecular structure of certolizumab pegol

A brief overview of the various technologies are presented in Section 3. Although specific details regarding the molecular structure are provided in Section 3.1, UCB would request that additional clarification is provided for the structure of certolizumab pegol, which is highly different to the other monoclonal antibodies it is listed alongside.

Certolizumab pegol is the only PEGylated Fab', Fc-free anti-TNF. The addition of the PEG part of the certolizumab pegol molecule increases the stability and half-life of certolizumab pegol, allowing the Fc-free molecule to have a similar half-life to a full antibody (14.4 days).[7]

PEGylation may also aid retention in inflamed tissue, and CZP has been shown to preferentially accumulate in inflamed tissue in animal models. A study in naïve mice and mice with ongoing collagen-induced arthritis used fluorescently labelled CZP and ADA to show that both anti-TNF therapies achieved greater penetration into arthritic paws compared to normal tissue.[8, 9]

Although certolizumab pegol has not been approved for use in pregnancy,[1] pre-clinical and clinical data suggest a lack of active placental transfer of certolizumab pegol which may be the consequence of the absence of an Fc region. Pre-clinical data showed that an anti-TNFα PEGylated Fab' fragment was undetectable or only detectable at a very low level in rodent foetal samples.[10] An *ex vivo* placental transfer study found that in 6 human placentas, certolizumab pegol levels in the foetal circulation were consistently below levels of the anti-D IgG control.[11] An independent investigator-driven study measuring placental transfer in 10 pregnant women treated with certolizumab pegol reported that certolizumab pegol levels in the cord blood and infant blood on the day of birth were consistently lower than those in maternal blood, suggesting low placental transfer. In some cases, certolizumab pegol

levels in cord and infant blood were below levels of detection.[12, 13] The European label for certolizumab pegol states that there are no adequate data from the use of certolizumab pegol in pregnant women.[1]

UCB would request that the wording around the certolizumab pegol molecule be revised to acknowledge its unique molecular structure, being Fc-free and PEGylated.

2 General responses

2.1 Marketing authorisations

In section 1.1 of the ACD, it is stated that "*Adalimumab, certolizumab pegol, etanercept and golimumab are recommended within their marketing authorisations, as treatment options for active ankylosing spondylitis*". We suggest this state "*severe active ankylosing spondylitis*", since this is the wording used in the summary of product characteristics of all the anti-TNFs (NB. this also applies to p.64).[1, 14-16]

In section 1.3 of the ACD, it is stated that "*Adalimumab, certolizumab pegol and etanercept are recommended within their marketing authorisations, as treatment options for non-radiographic axial spondyloarthritis*". We suggest this state "*severe non-radiographic axial spondyloarthritis*", since this is the definition used in the SPC of all the relevant anti-TNFs.[1, 14, 16]

2.2 Treatment recommendations

In Section 1.5, it is stated: "*The response to adalimumab, certolizumab pegol, etanercept or golimumab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response*".

UCB would like to highlight that current clinical practice suggests an evaluation period between weeks 12 and 24 and would suggest that any treatment recommendations are validated with the ongoing updates to the British Society of Rheumatology clinical guidelines for axSpA.

UCB would therefore suggest that the wording in this treatment recommendation be modified to offer more clinical discretion at the 12 week decision point.

2.3 The importance of extra-articular manifestations in axSpA

In Section 1.4 it is stated: "*The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available, and may include consideration of associated conditions*."

UCB agrees that extra-articular manifestations are an important consideration when selecting an anti-TNF for the treatment of axSpA, given the frequency of extra-articular manifestations in such patients. To this point, UCB refers to the data provided in their original submission, indicating the efficacy of certolizumab pegol for the improvement of the symptoms of such manifestations of axSpA, including uveitis, enthesitis and extra-spinal joints (see Sections 5.48 and 5.4.9).[17, 18]

During the 24 week double-blind phase of RAPID-axSpA, the incidence rate of uveitis flares was lower in certolizumab pegol-treated patients than placebo-treated patients, both in the overall population and between patients with a history of uveitis at baseline. Incidence of uveitis remained low to Week 96.

Certolizumab pegol-treated patients showed improvements in enthesitis, swollen joints and tender joints at Week 12 and Week 24 compared with placebo-treated patients, which were maintained to Week 96.

2.4 Sequential use of anti-TNFs in axSpA

Section 4.12 states: "*The Assessment Group concluded that, despite a decrease in response rates, sequential treatment with TNF-alpha inhibitors can be beneficial for people with ankylosing spondylitis.*"

The Committee acknowledges the dearth of robust clinical evidence to support the use of sequential treatment with anti-TNFs, stating that the most compelling data are that from the DANBIO registry. UCB would like to reiterate that sequential use of anti-TNFs is likely to be beneficial to a number of axSpA patients. Data from other rheumatic indications show that many patients will eventually lose response to their first anti-TNF (secondary loss of response), likely due to anti-drug antibodies. These patients

generally respond well to a second anti-TNF.[19] Hence, a strong patient need exists for sequential use of anti-TNFs in axSpA, amongst those losing response to an initial anti-TNF to regain improvements in disease activity, given that there are no other approved treatment options once a patient has failed NSAIDs.

UCB further wish to highlight that limited data from the RAPID-axSpA study also suggest that the treatment response to certolizumab pegol is not different between anti-TNF naïve and experienced patients (anti-TNF experienced patients excluded patients with no initial response to an anti-TNF [ie. primary failure] but included patients who had discontinued an anti-TNF for reasons other than primary failure [eg. secondary failure]);[20] ASAS40 responses and improvements in BASDAI scores were maintained on long-term in both anti-TNF naïve and experienced patients. While these results should be interpreted with caution given the low patient numbers in these analyses, they do add to the existing evidence base and support the efficacy of sequential treatment with anti-TNFs.

UCB would request that the data covering sequential use of a second-line anti-TNF in the limited case of loss-of-response be re-considered.

2.5 Comment on the relevance of trial data to clinical practice

In Section 4.14, it is stated: "*When TNF-alpha inhibitors were considered as a class, with 1 treatment effect, the meta-analysis showed statistically significant improvements compared with placebo at 10–16 weeks for all outcomes (Table 3). The Assessment Group reported that statistical heterogeneity was apparent in the analyses, and therefore the reliability of the pooled estimates, and their true relevance to people seen in clinical practice, is questionable. Estimates of the class effect of TNF-alpha inhibitors were consistently smaller in non-radiographic axial spondyloarthritis compared against those observed in ankylosing spondylitis trials*".

UCB recognises the rationale for treating the anti-TNF agents as a single class, however, several comments related to this statement need to be considered:

- The RAPID-axSpA trial is highly relevant to the UK clinical practice, being the only study to date to purposefully recruit across the spectrum of patients with active axSpA, including both AS and nr-axSpA sub-populations. The study design allowed for a direct comparison of baseline disease burden, quality of life and work-related productivity and treatment response between these sub-populations. Data from the RAPID-axSpA study showed a similar high disease burden and demonstrated comparable treatment effect between the AS and nr-axSpA sub-populations.[4]
- It is also worth noting that in RAPID-axSpA, nr-axSpA patients were recruited with objective signs of inflammation (as defined by sacroiliitis on MRI and/or elevated CRP) in line with the licence population.[4] We would therefore suggest that the wording in Section 4.14 be revised to acknowledge that the difference in treatment effect between AS and nr-axSpA subpopulations was not observed in all trials, for example: "*Estimates of the class effect of TNF-alpha inhibitors were consistently smaller in non-radiographic axial spondyloarthritis compared against those observed in ankylosing spondylitis trials, except in the Rapid-axSpA trial, where a similar treatment effect was observed between patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis*".

2.6 Comment on manufacturer ICERs

In Section 4.31, it is stated: "*Although there was consistency across the companies' ICER estimates for the ankylosing spondylitis population, the Assessment Group considered them (and the ICERs reported for people with non-radiographic axial spondyloarthritis) to be both speculative and uncertain.*"

While UCB acknowledge that generally ICERs are a result of modelling assumptions and subject to a level of uncertainty, and thus need to be tested through sensitivity analyses, UCB disagrees with the above comment on the speculative nature and high uncertainty of the ICERs.

The uncertainty within the submitted models was explored through extensive sensitivity analysis, so although some uncertainty always exists within a model, this has at least been explored and quantified. Furthermore, the submitted models obtained remarkably similar ICERs for the AS subpopulation under differing assumptions in terms of rebound, BASDAI/BASFI progression and other structural modelling

uncertainties. The observation that the York model provided similar ICERs also in the AS subpopulation serves as additional evidence for the robustness of ICERs under the numerous uncertainties.

UCB request the Committee to revise their wording to reflect the consistency of the ICERs while reducing the emphasis that they are speculative and highly uncertain in the AS sub-population.

2.7 Accuracies in reporting the UCB cost-effectiveness model

2.7.1 Week 24 response criteria

In Section 4.28, it is stated: "*All models included response criteria to decide whether TNF-alpha inhibitors were continued or withdrawn. The criteria were ASAS 20, ASAS 40 or BASDAI 50 at week 12, with the exception of company UCB which used response criteria at week 24.*"

UCB would like to clarify that, as per our original submission, the Week 24 response criteria was only used as the base case assumption for the AS sub-population, and that a sensitivity analysis at Week 12 was conducted in order to explore this model assumption. For the nr-axSpA sub-population, a 12 week response criteria was used, reflecting the availability of data at this time point across the included clinical trials.

UCB would therefore request this paragraph to be revised to accurately reflect the submitted evidence: "*All models included response criteria to decide whether TNF-alpha inhibitors were continued or withdrawn. The criteria were ASAS 20, ASAS 40 or BASDAI 50 at week 12, with the exception of company UCB, which used response criteria at week 24 for its base case model in the ankylosing spondylitis population.*"

2.7.2 Base case ICERs

In Section 4.29, and Tables 6 and 7, p.30, ICERs for the anti-TNFs from the various manufacturer models are presented in both the AS and nr-axSpA sub-populations.

UCB would request that the text in Section 4.29, and in Tables 6 and 7, be revised to highlight that the ICERs presented are from the base case analyses of AS and nr-axSpA submitted by manufacturers.

2.7.3 Response criteria justification (AS)

In Table 4, p.28, the response criteria justification for UCB's model is reported as "*RAPID-axSpA primary*".

UCB would request this be updated to "*RAPID-axSpA primary endpoint*" to accurately reflect that the information refers to the study endpoint.

2.7.4 Annual rate of withdrawal (long-term) (AS)

In Table 4, p.28, we would suggest that the Annual rate of withdrawal (long term) indicate that these are the assumptions applied to all anti-TNFs in each model, to make a clear distinction between the models developed by AbbVie, MSD and UCB, from the assumptions made by Pfizer, which was applied to etanercept only.

2.7.5 Model type (nr-axSpA)

In Table 5, p.29, the model type presented for UCB's model is "*Markov model*".

UCB would request this be revised to "*Decision tree followed by Markov model*" to accurately reflect the evidence from the UCB original submission.

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